(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 April 2004 (01.04.2004)

PCT

(10) International Publication Number
WO 2004/026888 A2

(51) International Patent Classification[7]: C07H

(21) International Application Number:
PCT/US2003/029577

(22) International Filing Date:
19 September 2003 (19.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/412,479 19 September 2002 (19.09.2002) US

(71) Applicants *(for all designated States except US)*: **COLEY PHARMACEUTICAL GMBH** [DE/DE]; Elisabeth-Selbert-Strasse 9, 40764 Langenfeld (DE). **UNIVERSITY OF SASKATCHEWAN** [CA/CA]; Kirk Hall, 117 Science Place, Saskatoon, Saskatchewan S7N 5C8 (CA). **QIAGEN GMBH** [DE/DE]; Max-Volmer-Strasse 4, 40724 Hilden (DE).

(72) Inventors; and

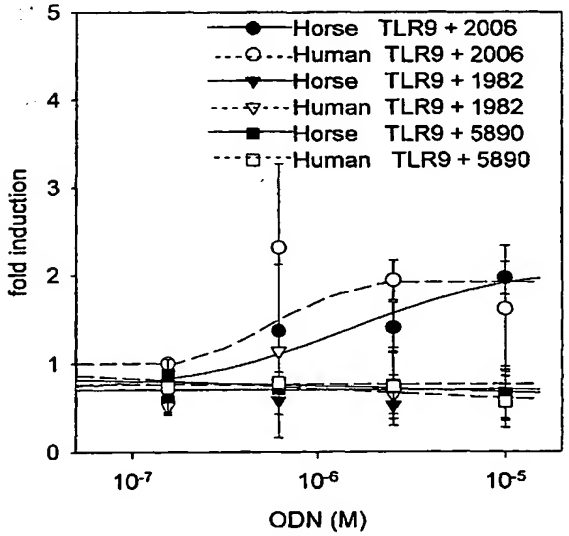
(75) Inventors/Applicants *(for US only)*: **LIPFORD, Grayson, B.** [US/US]; 38 Bates Road, Watertown, MA 02472 (US). **MOOKHERJEE, Neeloffer** [IN/CA]; Apt 408, 2233 Allison Road,, Vancouver, BC V6T IT7 (CA). **BABIUK, Lorne** [CA/CA]; 245 East Place, Saskatoon, Saskatchewan S7J 2Y1 (CA). **BROWNLIE, Robert** [CA/CA]; 123 O'Brien Crescent, Saskatoon, Saskatchewan S7K 5K3 (CA). **GRIEBEL, Philip** [CA/CA]; Box 36, RR5, Saskatoon, Saskatchewan S7K 3J8 (CA). **MUTWIRI, George** [CA/CA]; 569 Nordstrum Road, Saskatoon, Saskatchewan S7K 7X6 (CA). **HECKER, Rolf** [DE/DE]; Benrodestr. 60, 40597 Düsseldorf (DE).

(74) Agent: **STEELE, Alan, W.**; Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA 02210 (US).

(81) Designated States *(national)*: AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,

[Continued on next page]

(54) Title: TOLL-LIKE RECEPTOR 9 (TLR9) FROM VARIOUS MAMMALIAN SPECIES



(57) Abstract: Novel amino acid and nucleotide sequences for rat, pig (porcine), cow (bovine), horse (equine), and sheep (ovine) Toll-like receptor 9 (TLR9) are provided. Also provided are amino acid and nucleotide sequences for dog (canine), cat (feline), mouse (murine), and human TLR9. Comparison of these sequences, especially in combination with functional assessment for species-specific CpG motif preferences, permits identification of specific regions and amino acid residues of interest in TLR9 ligand interaction. Novel chimeric TLR9 receptor molecules, cells expressing these molecules, and methods for their use in screening assays for TLR9 ligands are also provided.

WO 2004/026888 A2

MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) **Designated States** *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

TOLL-LIKE RECEPTOR 9 (TLR9) FROM VARIOUS MAMMALIAN SPECIES

Background of the Invention

Synthetic oligodeoxynucleotides (ODN) and DNA containing immunostimulatory CpG motifs (CpG DNA) function as potent adjuvants and activators of the innate immune system. Heeg K et al. (2000) *Int Arch Allergy Immunol* 121:87-97; Krieg AM (2001) *Vaccine* 19:618-22. A wide variety of CpG-containing sequences have been screened for biological activity and it is reported that optimal CpG DNA sequences can vary among species. Rankin R et al. (2001) *Antisense Nucleic Acid Drug Dev* 11:333-40.

Toll-like receptor 9 (TLR9) has recently been identified as a receptor for CpG ODN. Hemmi H et al. (2000) *Nature* 408:740-5. The molecular mechanism by which TLR9 recognizes CpG DNA is not understood.

Summary of the Invention

Toll-like receptor 9 (TLR9) is known to be involved in innate immunity and to signal in response to CpG DNA. To date, the amino acid sequences only of human and murine TLR9 have been reported, and, interestingly, these two species are known to prefer different CpG motifs. The structural basis for this species-specific CpG motif preference has not yet been fully elucidated. The instant invention provides, in part, novel amino acid and nucleotide sequences of rat, pig, cow, and horse TLR9. These novel TLR9 sequences are useful for elucidating certain key structural features of TLR9. Specifically, comparison of sequences of murine, human, and these novel TLR9 sequences permits identification of areas of highly conserved sequence, areas of group conservation, and areas of hypervariability. In addition, such comparisons permit an assessment of evolutionary relatedness among TLR9 molecules of the various species, as well as an assessment of inter-species homologies. Importantly, such comparisons permit a rational basis for identifying amino acids in TLR9 that may be involved in the CpG binding site, as well as amino acids involved in conferring species specificity for particular CpG motifs. Such information may be used to design and construct novel TLR9 molecules which incorporate specific point or regional mutations and which possess desired ligand binding characteristics. Such information may also be useful in designing and identifying novel ligands for TLR9 of a given species.

In one aspect, the invention provides isolated polypeptides having amino acid sequences for rat, pig (porcine), cow (bovine), horse (equine), and sheep (ovine) TLR9 polypeptides. These amino acid sequences correspond to SEQ ID NOs 1, 5, 9, 13, and 17, respectively. Each of these sequences is believed to include at least a majority of an extracellular domain, as well as a transmembrane region and at least part of a TLR/IL-1 receptor (TIR) domain. To the extent any such sequence may lack an amino-terminal and/or carboxy-terminal sequence, such sequence is ascertainable, without undue experimentation, using conventional molecular biology techniques and the sequence information provided herein.

In another aspect the invention provides isolated polypeptides having amino acid sequences for essentially the whole extracellular domain, optionally including a signal peptide, of each of rat, porcine, bovine, equine, and ovine TLR9. These amino acid sequences correspond to SEQ ID NOs 2, 6, 10, 14, and 18, respectively. Such extracellular domains are believed to include sequence specifically involved in binding to TLR9 ligand, such as CpG DNA. In addition, such extracellular domains are believed to include sequence that confers species specificity for particular CpG motifs.

Isolated nucleic acid molecules encoding the polypeptides just described above are also provided according to further aspects of the invention. Such nucleic acid molecules include, but are not limited to, nucleic acid molecules having sequences provided by SEQ ID NOs 3, 7, 11, 15, 19; and 4, 8, 12, 16, and 20, respectively. Isolated nucleic acid molecules encoding the TLR9 polypeptides of SEQ ID NOs 1, 5, 9, 13, 17; and 2, 6, 10, 14, and 18 also include nucleic acid molecules that differ in sequence from SEQ ID NOs 3, 7, 11, 15, 19; and 4, 8, 12, 16, and 20, respectively, due to degeneracy of the genetic code. Such nucleic acid molecules will hybridize, under stringent conditions, with suitably selected nucleic acid molecules having sequences selected from SEQ ID NOs 3, 4, 7, 8, 11, 12, 15, 16, 19, and 20.

In another aspect the invention provides a vector which includes an isolated nucleic acid molecule of the invention. In one embodiment the vector is an expression vector and the isolated nucleic acid molecule of the invention is operably linked to a regulatory sequence in the vector. When present within a cell, an expression vector according to this aspect of the invention causes the cell to express a polypeptide of the invention.

The invention according to another aspect provides a cell in which a vector of the invention is present. In one embodiment the cell containing the vector expresses a

polypeptide of the invention. In certain embodiments the cell also contains a reporter construct that transduces a TLR9-mediated signal in response to contact of the polypeptide of the invention or a TLR9 with a suitable TLR9 ligand. The cell containing the vector, and optionally containing the reporter construct, can be used in screening methods also provided by the invention.

In yet another aspect the invention provides an antibody or antibody fragment that binds specifically to an isolated polypeptide of the invention. In certain embodiments the antibody or antibody fragment binds uniquely to one of rat, porcine, bovine, equine, or ovine TLR9 polypeptide. More specifically, the antibody or antibody fragment binds uniquely to one of the isolated polypeptides of the invention. In one embodiment the antibody or antibody fragment that binds uniquely to one of rat, porcine, bovine, equine, or ovine TLR9 polypeptide also binds to either mouse or human TLR9. In another embodiment the antibody or antibody fragment that binds uniquely to one of rat, porcine, bovine, equine, or ovine TLR9 polypeptide does not also bind to either mouse or human TLR9. In some embodiments the antibody or antibody fragment binds selectively to a chimeric TLR9 polypeptide of the invention. In certain embodiments the antibody or antibody fragment of the invention is a monoclonal antibody or fragment of a monoclonal antibody.

In one aspect the invention provides a method for identifying key amino acids in a TLR9 of a first species which confer specificity for CpG DNA optimized for TLR9 of the first species. The method involves aligning protein sequences of TLR9 of a first species, TLR9 of a second species, and TLR9 of a third species, wherein the TLR9 of the third species preferentially generates a signal when contacted with a CpG DNA optimized for TLR9 of the first species rather than when contacted with a CpG DNA optimized for TLR9 of the second species; generating an initial set of candidate amino acids in the TLR9 of the first species by excluding each amino acid in the TLR9 of the first species which (a) is identical with the TLR9 of the second species or (b) differs from the TLR9 of the second species only by conservative amino acid substitution; generating a refined set of candidate amino acids by selecting each amino acid in the initial set of candidate amino acids in the TLR9 of the first species which (a) is identical with the TLR9 of the third species or (b) differs from the TLR9 of the third species only by conservative amino acid substitution; and identifying as key amino acids in the TLR9 of the first species each amino acid in the refined set of candidate amino acids.

In another aspect the invention provides a method for identifying key amino acids in human TLR9 which confer specificity for CpG DNA optimized for human TLR9. The method according to this aspect of the invention involves aligning protein sequences of human TLR9, murine TLR9, and TLR9 of a third species, wherein the TLR9 of the third species preferentially generates a signal when contacted with a CpG DNA optimized for human TLR9 rather than when contacted with a CpG DNA optimized for murine TLR9; generating an initial set of candidate amino acids in human TLR9 by excluding each amino acid in human TLR9 which (a) is identical with murine TLR9 or (b) differs from murine TLR9 only by conservative amino acid substitution; generating a refined set of candidate amino acids by selecting each amino acid in the initial set of candidate amino acids in human TLR9 which (a) is identical with the TLR9 of the third species or (b) differs from the TLR9 of the third species only by conservative amino acid substitution; and identifying as key amino acids in human TLR9 each amino acid in the refined set of candidate amino acids. In one embodiment the method according to this aspect of the invention is performed iteratively with a plurality of TLR9s derived from different species other than human and mouse, wherein for each TLR9 the refined set of candidate amino acids is assigned a weight corresponding to a ratio equal to (responsiveness to human-preferred CpG DNA)/(responsiveness to murine-preferred CpG DNA).

In another aspect the invention also provides an isolated polypeptide having an amino acid sequence identical to SEQ ID NO:30 (extracellular domain (ECD) of murine TLR9) except for substitution of at least one key amino acid identified according to the method above. The polypeptide according to this aspect of the invention is a chimeric TLR9 polypeptide. Preferably the polypeptide according to this aspect of the invention binds to CpG DNA optimized for human TLR9 better than does the isolated polypeptide having an amino acid sequence identical to SEQ ID NO:30 (ECD of murine TLR9). In one embodiment the polypeptide includes only one substituted amino acid. The isolated polypeptide according to this aspect of the invention may further include sequence involved in TLR/IL-1R signal transduction, e.g., intracellular domain of TLR9 as provided in SEQ ID NOs 29 and 33. For example, in one embodiment a polypeptide according to this aspect of the invention is an isolated polypeptide having an amino acid sequence identical to SEQ ID NO:29 (full length murine TLR9) except for substitution of at least one key amino acid identified according to the method above.

In another aspect the invention provides an isolated nucleic acid molecule including a nucleic acid sequence encoding a chimeric TLR9 polypeptide just described. In one embodiment the isolated nucleic acid molecule has a nucleic acid sequence encoding a chimeric TLR9 polypeptide just described.

In yet another aspect, the invention provides a screening method to identify a TLR9 ligand. The method involves contacting a polypeptide (including a chimeric TLR9 polypeptide) of the invention with a candidate TLR9 ligand; measuring a signal in response to the contacting; and identifying the candidate TLR9 ligand as a TLR9 ligand when the signal in response to the contacting is consistent with TLR9 signaling. In one embodiment the candidate TLR9 ligand is an immunostimulatory nucleic acid. In one embodiment the candidate TLR9 ligand is a CpG DNA.

The invention also provides, in yet a further aspect, a screening method to identify species-specific CpG-motif preference of an isolated polypeptide of the invention. The method according to this aspect of the invention involves contacting an isolated polypeptide of the invention with a CpG DNA including a hexamer sequence selected from the group consisting of GACGTT, AACGTT, CACGTT, TACGTT, GGCGTT, GCCGTT, GTCGTT, GATGTT, GAAGTT, GAGGTT, GACATT, GACCTT, GACTTT, GACGCT, GACGAT, GACGGT, GACGTC, GACGTA, and GACGTG; measuring a signal in response to the contacting; and identifying a species-specific CpG-motif preference when the signal in response to the contacting is consistent with TLR9 signaling. In one embodiment the CpG DNA is an oligodeoxynucleotide having a sequence selected from the group consisting of

TCCATGACGTTTTTGATGTT (SEQ ID NO:39),
TCCATAACGTTTTTGATGTT (SEQ ID NO:40),
TCCATCACGTTTTTGATGTT (SEQ ID NO:41),
TCCATTACGTTTTTGATGTT (SEQ ID NO:42),
TCCATGGCGTTTTTGATGTT (SEQ ID NO:43),
TCCATGCCGTTTTTGATGTT (SEQ ID NO:44),
TCCATGTCGTTTTTGATGTT (SEQ ID NO:45),
TCCATGATGTTTTTGATGTT (SEQ ID NO:46),
TCCATGAAGTTTTTGATGTT (SEQ ID NO:47),
TCCATGAGGTTTTTGATGTT (SEQ ID NO:48),
TCCATGACATTTTTGATGTT (SEQ ID NO:49),
TCCATGACCTTTTTGATGTT (SEQ ID NO:50),
TCCATGACTTTTTTGATGTT (SEQ ID NO:51),
TCCATGACGCTTTTGATGTT (SEQ ID NO:52),
TCCATGACGATTTTGATGTT (SEQ ID NO:53),
TCCATGACGGTTTTGATGTT (SEQ ID NO:54),

TCCATGACGTCTTTGATGTT (SEQ ID NO:55),
TCCATGACGTATTTGATGTT (SEQ ID NO:56), and
TCCATGACGTGTTTGATGTT (SEQ ID NO:57).

In certain embodiments of the screening methods of the invention, the signal includes expression of a reporter gene responsive to TLR/IL-1R signal transduction pathway. In one embodiment the reporter gene is operatively linked to a promoter sensitive to NF-κB. In one embodiment the signal in response to contacting is binding of the candidate TLR9 ligand or CpG DNA to the polypeptide of the invention.

In one embodiment the screening method is performed on a plurality of test compounds. In one embodiment the response mediated by the TLR9 signal transduction pathway is measured quantitatively and the response mediated by the TLR9 signal transduction pathway associated with each of the plurality of test compounds is compared with a response arising as a result of an interaction between the functional TLR9 and a reference immunostimulatory compound.

Brief Description of the Figures

Figure 1 depicts a Clustal W multiple sequence alignment of deduced amino acid sequences for cat (feline), dog (canine), cow (bovine), mouse (murine), sheep (ovine), pig (porcine), horse (equine), human, and rat TLR9 polypeptides. The deduced amino acid sequences for feline, canine, bovine, murine, ovine, porcine, equine, human, and rat TLR9 polypeptides shown in the figure correspond to SEQ ID NOs 25, 21, 9, 29, 17, 5, 13, 33, and 1, respectively. Lines labeled "multiple" refer to the multiple sequence alignment of all six sequences shown. Lines labeled "mo/hu" refer to a paired sequence alignment of mouse and human TLR9 sequences alone.

Figure 2 is a cladogram depicting an evolutionary relatedness tree for rat, murine, porcine, bovine, equine, and human TLR9 polypeptides in Figure 1.

Figure 3 is a graph depicting species specificity of TLR9 signaling with selected oligonucleotides having strong specificity for human (2006), mouse (5890), or neither (1982).

Detailed Description of the Invention

The present invention provides novel amino acid and nucleotide sequences for TLR9 derived from rat, pig, cow, horse, and sheep. These sequences can be used to identify key features of the primary sequences of these and related TLR molecules, including previously

known primary sequences of human and mouse (murine) TLR9. Such key features include binding site information and species specificity toward particular CpG motifs. Native and novel chimeric TLR9 polypeptides designed with the aid of this information can be expressed in vitro or in vivo and used in screening assays to identify and to design novel TLR9 ligands. Additionally, the native and novel chimeric TLR9 polypeptides designed with the aid of this information can be expressed in vitro or in vivo and used in screening assays to compare various TLR9 ligands, including CpG DNA.

In one aspect the invention provides isolated TLR9 polypeptides, and isolated nucleic acid molecules encoding them, from rat, pig, cow, horse, and sheep. The term "isolated" as used herein with reference to a nucleic acid molecule or polypeptide means substantially free of or separated from components with which it is normally associated in nature, e.g., other nucleic acids, proteins, lipids, carbohydrates or *in vivo* systems to an extent practical and appropriate for its intended use. In particular, the nucleic acids or polypeptides are sufficiently pure and are sufficiently free from other biological constituents of host cells so as to be useful in, for example, producing pharmaceutical preparations. Because an isolated nucleic acid or polypeptide of the invention may be admixed with a pharmaceutically acceptable carrier in a pharmaceutical preparation, the nucleic acid or polypeptide may represent only a small percentage by weight of such a preparation. The nucleic acid or polypeptide is nonetheless substantially pure in that it has been substantially separated from the substances with which it may be associated in living systems.

An amino acid sequence of rat TLR9 is provided as SEQ ID NO:1. Based on comparison with known amino acid sequences of human and murine TLR9, it appears that SEQ ID NO:1 includes sequence for at least a majority of the extracellular domain, all of the transmembrane domain, and at least a portion of the intracellular domain of rat TLR9 (See Figure 1). Amino acids numbered 1-821 of SEQ ID NO:1 are presumptively extracellular domain and correspond to SEQ ID NO:2. SEQ ID NO:3 is a nucleotide sequence of rat TLR9 cDNA having an open reading frame corresponding to nucleotides 1-3096. SEQ ID NO:4 is a nucleotide sequence of rat cDNA encoding amino acids 1-821 of SEQ ID NO:1.

An amino acid sequence of porcine TLR9 is provided as SEQ ID NO:5. Based on comparison with known amino acid sequences of human and murine TLR9, it appears that SEQ ID NO:5 includes sequence for at least a majority of the extracellular domain, all of the transmembrane domain, and at least a portion of the intracellular domain of porcine TLR9

(See Figure 1). Amino acids numbered 1-819 of SEQ ID NO:5 are presumptively extracellular domain and correspond to SEQ ID NO:6. SEQ ID NO:7 is a nucleotide sequence of porcine TLR9 cDNA having an open reading frame corresponding to nucleotides 77-3166. SEQ ID NO:8 is a nucleotide sequence of porcine cDNA encoding amino acids 1-819 of SEQ ID NO:5.

An amino acid sequence of bovine TLR9 is provided as SEQ ID NO:9. Based on comparison with known amino acid sequences of human and murine TLR9, it appears that SEQ ID NO:9 includes sequence for at least a majority of the extracellular domain, all of the transmembrane domain, and at least a portion of the intracellular domain of bovine TLR9 (See Figure 1). Amino acids numbered 1-818 of SEQ ID NO:9 are presumptively extracellular domain and correspond to SEQ ID NO:10. SEQ ID NO:11 is a nucleotide sequence of bovine TLR9 cDNA having an open reading frame corresponding to nucleotides 84-3170. SEQ ID NO:12 is a nucleotide sequence of bovine cDNA encoding amino acids 1-818 of SEQ ID NO:9.

An amino acid sequence of equine TLR9 is provided as SEQ ID NO:13. Based on comparison with known amino acid sequences of human and murine TLR9, it appears that SEQ ID NO:13 includes sequence for at least a majority of the extracellular domain, all of the transmembrane domain, and at least a portion of the intracellular domain of equine TLR9 (See Figure 1). Amino acids numbered 1-820 of SEQ ID NO:13 are presumptively extracellular domain and correspond to SEQ ID NO:14. SEQ ID NO:15 is a nucleotide sequence of equine TLR9 cDNA having an open reading frame corresponding to nucleotides 115-3207. SEQ ID NO:16 is a nucleotide sequence of equine cDNA encoding amino acids 1-820 of SEQ ID NO:13.

An amino acid sequence of ovine TLR9 is provided as SEQ ID NO:17. Based on comparison with known amino acid sequences of human and murine TLR9, it appears that SEQ ID NO:17 includes sequence for at least a majority of the extracellular domain, all of the transmembrane domain, and at least a portion of the intracellular domain of ovine TLR9 (See Figure 1). Amino acids numbered 1-818 of SEQ ID NO:17 are presumptively extracellular domain and correspond to SEQ ID NO:18. SEQ ID NO:19 is a nucleotide sequence of ovine TLR9 cDNA having an open reading frame corresponding to nucleotides 92-3178. SEQ ID NO:20 is a nucleotide sequence of ovine cDNA encoding amino acids 1-818 of SEQ ID NO:17.

SEQ ID NO:1 (Rat TLR9)

MVLCRRTLHPLSLLVQAAVLAEALALGTLPAFLPCELKPHGLVDCNWLFLKSVPHFSAAEPRSNITSLSLIANRI
HHLHNLDFVHLPNVRQLNLKWNCPPPGLSPLHFSCRMTIEPKTFLAMRMLEELNLSYNGITTVPRLPSSLTNLSL
SHTNILVLDASSLAGLHSLRVLFMDGNCYYKNPCNGAVNVTPDAFLGLSNLTHLSLKYNNLTEVPRQLPPSLEYL
LLSYNLIVKLGAEDLANLTSLRMLDVGGNCRRCDHAPDLCTECRQKSLDLHPQTFHHLSHLEGLVLKDSSLHSLN
SKWFQGLANLSVLDLSENFLYESINKTSAFQNLTRLRKLDLSFNYCKKVSFARLHLASSFKSLVSLQELNMNGIF
FRLLNKNTLRWLAGLPKLHTLHLQMNFINQAQLSVFSTFRALRFVDLSNNRISGPPTLSRVAPEKADEAEKGVPW
PASLTPALPSTPVSKNFMVRCKNLRFTMDLSRNNQVTIKPEMFVNLSHLQCLSLSHNCIAQAVNGSQFLPLTNLK
VLDLSYNKLDLYHSKSFSELPQLQALDLSYNSQPFSMQGIGHNFSFLANLSRLQNLSLAHNDIHSRVSSRLYSTS
VEYLDFSGNGVGRMWDEEDLYLYFFQDLRSLIHLDLSQNKLHILRPQNLNYLPKSLTKLSFRDNHLSFFNWSSLA
FLPNLRDLDLAGNLLKALTNGTLPNGTLLQKLDVSSNSIVFVVPAFFALAVELKEVNLSHNILKTVDRSWFGPIV
MNLTVLDVSSNPLHCACGAPFVDLLLEVQTKVPGLANGVKCGSPRQLQGRSIFAQDLRLCLDDVLSRDCFGLSLL
AVAVGTVLPLLQHLCGWDVWYCFHLCLAWLPLLTRGRRSAQALPYDAFVVFDKAQSAVADWVYNELRVRLEERRG
RRALRLCLEDRDWLPGQTLFENLWASIYGSRKTLFVLAHTDKVSGLLRTSFLLAQQRLLEDRKDVVVLVILRPDA
HRSRYVRLRQRLCRQSVLFWPHQPNGQGSFWAQLSTALTRDNHHFYNRNFCRGPTAE

SEQ ID NO:2 (Rat TLR9)

MVLCRRTLHPLSLLVQAAVLAEALALGTLPAFLPCELKPHGLVDCNWLFLKSVPHFSAAEPRSNITSLSLIANRI
HHLHNLDFVHLPNVRQLNLKWNCPPPGLSPLHFSCRMTIEPKTFLAMRMLEELNLSYNGITTVPRLPSSLTNLSL
SHTNILVLDASSLAGLHSLRVLFMDGNCYYKNPCNGAVNVTPDAFLGLSNLTHLSLKYNNLTEVPRQLPPSLEYL
LLSYNLIVKLGAEDLANLTSLRMLDVGGNCRRCDHAPDLCTECRQKSLDLHPQTFHHLSHLEGLVLKDSSLHSLN
SKWFQGLANLSVLDLSENFLYESINKTSAFQNLTRLRKLDLSFNYCKKVSFARLHLASSFKSLVSLQELNMNGIF
FRLLNKNTLRWLAGLPKLHTLHLQMNFINQAQLSVFSTFRALRFVDLSNNRISGPPTLSRVAPEKADEAEKGVPW
PASLTPALPSTPVSKNFMVRCKNLRFTMDLSRNNQVTIKPEMFVNLSHLQCLSLSHNCIAQAVNGSQFLPLTNLK
VLDLSYNKLDLYHSKSFSELPQLQALDLSYNSQPFSMQGIGHNFSFLANLSRLQNLSLAHNDIHSRVSSRLYSTS
VEYLDFSGNGVGRMWDEEDLYLYFFQDLRSLIHLDLSQNKLHILRPQNLNYLPKSLTKLSFRDNHLSFFNWSSLA
FLPNLRDLDLAGNLLKALTNGTLPNGTLLQKLDVSSNSIVFVVPAFFALAVELKEVNLSHNILKTVDRSWFGPIV
MNLTVLDVSSNPLHCACGAPFVDLLLEVQTKVPGLANGVKCGSPRQLQGRSIFAQDLRLCLDDVLSRDCFG

SEQ ID NO:3 (Rat TLR9)

atggttctctgtcgcaggaccctgcacccttgtctctcctggtacaggccgcagtgctggctgaggctctggcc
ctgggtaccctgcctgccttcctaccctgtgaactgaagcctcatggcctggtagactgcaactggctcttcctg
aagtctgtgcctcacttctctgccgcagaaccccgttccaacatcaccagcctttccttgatcgccaaccgcatc
caccacctgcacaacctcgactttgtccacctgcccaacgtgcgacagctgaacctcaagtggaactgtccgccc
cctggcctcagccccttgcacttctcctgccgcatgaccattgagcccaaaaccttcctggctatgcgcatgctg
gaagagctgaacctgagctataacggtatcaccactgtgccccgcctgcccagctccctgacgaatctgagccta
agccacaccaacatcctggtactcgatgccagcagcctcgctggcctgcacagcctgcgagttctcttcatggac
gggaactgctactacaagaacccctgcaacggggcggtgaacgtgaccccggacgccttcctgggcttgagcaac
ctcacccacttgtcccttaagtataacaacctcacagaggtgccccgccaactgccccccagcctggagtacctc
ctgctgtcctataacctcatcgtcaagctgggggccgaagacctagccaacctgacctcccttcgaatgcttgat
gtgggtgggaattgccgtcgctgtgatcacgcccccgacctctgtacagaatgccggcagaagtcccttgatctg
caccctcagactttccatcacctgagccaccttgaaggcctggtgctgaaggacagttctctccactcgctgaac
tccaagtggttccagggtctggcgaacctctcggtgctggacctaagcgagaactttctctacgagagcatcaac
aaaaccagcgcctttcagaacctgacccgtctgcgcaagctcgacctgtccttcaattactgcaagaaggtatcg
ttcgcccgcctccacctggcaagttccttcaagagcctggtgtcgctgcaggagctgaacatgaacggcatcttc
ttccgcttactcaacaagaacacgctcaggtggctggctggtctgcccaagctccacacgctgcaccttcaaatg
aatttcatcaaccaggcgcagctcagcgtctttagtaccttccgagcccttcgctttgtggacctgtccaataat
cgcatcagcgggcctccaacgctgtccagagtcgcccccgaaaaggcagacgaggcggagaaggggttccatgg
cctgcaagtctcaccccagctctcccgagcactcccgtctcaaagaacttcatggtcaggtgtaagaacctcaga
ttcaccatggacctgtctcggaacaaccaggtgactatcaagccagagatgttcgtcaacctctcccatctccag
tgtctgagcctgagccacaactgcatcgcgcaggctgtcaatggctctcagttcctgccgctgaccaacctgaag
gtgctggacctgtcctataacaagctggacctgtaccattcgaaatcgttcagtgagctcccacagttgcaggcc

ctggacctgagctacaacagccagccattcagcatgcaggggataggccacaacttcagttttctggccaatctg
tccaggttacagaaccttagcctggcacacaatgacattcacagccgcgtgtcctcacgcctctacagcacctca
gtggagtatctggacttcagcggcaacggtgtgggccgcatgtgggacgaggaggacctttacctctatttcttc
caagacctgagaagcctgattcatctggacctgtctcagaataagctgcacatcctccggccccagaacctcaac
tacctccccaagagcctgacgaagctgagtttccgtgacaatcacctctctttctttaactggagcagtctggcc
ttcctgcccaatctgcgagacctggacctggcaggcaatctactaaaggccctgaccaacggcaccctgcctaat
ggcacgctcctccagaaactggatgtcagtagcaacagtatcgtctttgtggtcccagccttctttgctctggcg
gtagagctaaaagaggtcaacctcagccataacatcctcaagactgtggatcgctcctggtttgggcccattgtg
atgaacctgacggttctagacgtgagcagcaaccctctgcattgtgcctgcggtgcacccttgtagacttactg
ctggaagtgcagaccaaggtgcctggcctggctaacggtgtgaagtgtggcagtccccgccagctgcagggccgc
agcatctttgcgcaagacctgcggctgtgcctggatgacgtcctttctcgggactgctttggcctttcactcctg
gctgtggccgtgggcacggtgttgccttactgcagcatctctgcggctgggacgtctggtactgtttccatctg
tgcctggcatggctacctttgctgacccgtggccggcgcagcgcccaagctctcccttatgatgccttcgtggtg
ttcgataaggcgcagagcgcggttgctgactgggtgtataacgagcttcgagtgcggctagaggagcggcgcggt
cgccgagccctacgcttgtgtctggaggaccgagattggctgcctggccagacactcttcgagaacctctgggcc
tccatctatggcagccgcaagactctgtttgtgctggcccacacggacaaggtcagtggcctcctgcgcaccagc
ttcctgctggctcagcagcgcctgctggaggaccgcaaggacgtggtggtgttggtgatcctgcgcccctgatgcc
caccgctcccgctacgtgcgactgcgccagcgcctctgccgccagagtgtgctcttctggccccatcagcccaac
gggcagggcagcttctgggcccagctgagtacagccctgactagggacaaccaccacttctataaccggaacttc
tgccggggacctacagcagaatag

SEQ ID NO:4 (Rat TLR9)

atggttctctgtcgcaggaccctgcacccttgtctctcctggtacaggccgcagtgctggctgaggctctggcc
ctgggtaccctgcctgccttcctaccctgtgaactgaagcctcatggcctggtagactgcaactggctcttcctg
aagtctgtgcctcacttctctgccgcagaaccccgttccaacatcaccagcctttccttgatcgccaaccgcatc
caccacctgcacaacctcgactttgtccacctgcccaacgtgcgacagctgaacctcaagtggaactgtccgccc
cctggcctcagccccttgcacttctcctgccgcatgaccattgagcccaaaaccttcctggctatgcgcatgctg
gaagagctgaacctgagctataacggtatcaccactgtgccccgcctgcccagctccctgacgaatctgagccta
agccacaccaacatcctggtactcgatgccagcagcctcgctggcctgcacagcctgcgagttctcttcatggac
gggaactgctactacaagaacccctgcaacggggcggtgaacgtgaccccggacgccttcctgggcttgagcaac
ctcacccacttgtcccttaagtataacaacctcacagaggtgccccgccaactgccccccagcctggagtacctc
ctgctgtcctataacctcatcgtcaagctgggggccgaagacctagccaacctgacctcccttcgaatgcttgat
gtgggtgggaattgccgtcgctgtgatcacgcccccgacctctgtacagaatgccggcagaagtcccttgatctg
caccctcagactttccatcacctgagccaccttgaaggcctggtgctgaaggacagttctctccactcgctgaac
tccaagtggttccagggtctggcgaacctctcggtgctggacctaagcgagaactttctctacgagagcatcaac
aaaaccagcgcctttcagaacctgacccgtctgcgcaagctcgacctgtccttcaattactgcaagaaggtatcg
ttcgcccgcctccacctggcaagttccttcaagagcctggtgtcgctgcaggagctgaacatgaacggcatcttc
ttccgcttactcaacaagaacacgctcaggtggctggctggtctgcccaagctccacacgctgcaccttcaaatg
aatttcatcaaccaggcgcagctcagcgtctttagtaccttccgagcccttcgctttgtggacctgtccaataat
cgcatcagcgggcctccaacgctgtccagagtcgccccgaaaaggcagacgaggcggagaaggggttccatgg
cctgcaagtctcaccccagctctcccgagcactcccgtctcaaagaacttcatggtcaggtgtaagaacctcaga
ttcaccatggacctgtctcggaacaaccaggtgactatcaagccagagatgttcgtcaacctctcccatctccag
tgtctgagcctgagccacaactgcatcgcgcaggctgtcaatggctctcagttcctgccgctgaccaacctgaag
gtgctggacctgtcctataacaagctggacctgtaccattcgaaatcgttcagtgagctcccacagttgcaggcc
ctggacctgagctacaacagccagccattcagcatgcaggggataggccacaacttcagttttctggccaatctg
tccaggttacagaaccttagcctggcacacaatgacattcacagccgcgtgtcctcacgcctctacagcacctca
gtggagtatctggacttcagcggcaacggtgtgggccgcatgtgggacgaggaggacctttacctctatttcttc
caagacctgagaagcctgattcatctggacctgtctcagaataagctgcacatcctccggccccagaacctcaac
tacctccccaagagcctgacgaagctgagtttccgtgacaatcacctctctttctttaactggagcagtctggcc
ttcctgcccaatctgcgagacctggacctggcaggcaatctactaaaggccctgaccaacggcaccctgcctaat
ggcacgctcctccagaaactggatgtcagtagcaacagtatcgtctttgtggtcccagccttctttgctctggcg
gtagagctaaaagaggtcaacctcagccataacatcctcaagactgtggatcgctcctggtttgggcccattgtg
atgaacctgacggttctagacgtgagcagcaaccctctgcattgtgcctgcggtgcacccttgtagacttactg
ctggaagtgcagaccaaggtgcctggcctggctaacggtgtgaagtgtggcagtccccgccagctgcagggccgc
agcatctttgcgcaagacctgcggctgtgcctggatgacgtcctttctcgggactgctttggc

SEQ ID NO:5 (Porcine TLR9)

MGPRCTLHPLSLLVQVTALAAALAQGRLPAFLPCELQPHGLVNCNWLFLKSVPHFSAAAPRANVTSLSLLSNRIH
HLHDSDFVHLSSLRTLNLKWNCPPAGLSPMHFPCHMTIEPNTFLAVPTLEELNLSYNSITTVPALPDSLVSLSLS
RTNILVLDPTHLTGLHALRYLYMDGNCYYKNPCQGALEVVPGALLGLGNLTHLSLKYNNLTEVPRSLPPSLETLL
LSYNHIVTLTPEDLANLTALRVLDVGGNCRRCDHARNPCRECPKDHPKLHSDTFSHLSRLEGLVLKDSSLYNLDT
RWFRGLDRLQVLDLSENFLYDCITKTTAFQGLARLRSLNLSFNYHKKVSFAHLHLAPSFGHLRSLKELDMHGIFF
RSLSETTLQPLVQLPMLQTLRLQMNFINQAQLSIFGAFPGLLYVDLSDNRISGAARPVAITREVDGRERVWLPSR
NLAPRPLDTLRSEDFMPNCKAFSFTLDLSRNNLVTIQSEMFARLSRLECLRLSHNSISQAVNGSQFVPLTSLRVL
DLSHNKLDLYHGRSFTELPRLEALDLSYNSQPFTMQGVGHNLSFVAQLPALRYLSLAHNDIHSRVSQQLCSASLC
ALDFSGNDLSRMWAEGDLYLRFFQGLRSLVWLDLSQNHLHTLLPRALDNLPKSLKHLHLRDNNLAFFNWSSLTLL
PKLETLDLAGNQLKALSNGSLPSGTQLRRLDLSGNSIGFVNPGFFALAKQLEELNLSANALKTVEPSWFGSMVGN
LKVLDVSANPLHCACGATFVGFLLEVQAAVPGLPSRVKCGSPGQLQGHSIFAQDLRLCLDETLSWNCFGISLLAM
ALGLVVPMLHHLCGWDLWYCFHLCLAWLPHRGQRRGADALFYDAFVVFDKAQSAVADWVYNELRVQLEERRGRRA
LRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRLLEDRKDVVVLVILRPDAYRS
RYVRLRQRLCRQSVLLWPHQPRGQGSFWAQLGTALTRDNHHFYNRNFCRGPTTAE

SEQ ID NO:6 (Porcine TLR9)

MGPRCTLHPLSLLVQVTALAAALAQGRLPAFLPCELQPHGLVNCNWLFLKSVPHFSAAAPRANVTSLSLLSNRIH
HLHDSDFVHLSSLRTLNLKWNCPPAGLSPMHFPCHMTIEPNTFLAVPTLEELNLSYNSITTVPALPDSLVSLSLS
RTNILVLDPTHLTGLHALRYLYMDGNCYYKNPCQGALEVVPGALLGLGNLTHLSLKYNNLTEVPRSLPPSLETLL
LSYNHIVTLTPEDLANLTALRVLDVGGNCRRCDHARNPCRECPKDHPKLHSDTFSHLSRLEGLVLKDSSLYNLDT
RWFRGLDRLQVLDLSENFLYDCITKTTAFQGLARLRSLNLSFNYHKKVSFAHLHLAPSFGHLRSLKELDMHGIFF
RSLSETTLQPLVQLPMLQTLRLQMNFINQAQLSIFGAFPGLLYVDLSDNRISGAARPVAITREVDGRERVWLPSR
NLAPRPLDTLRSEDFMPNCKAFSFTLDLSRNNLVTIQSEMFARLSRLECLRLSHNSISQAVNGSQFVPLTSLRVL
DLSHNKLDLYHGRSFTELPRLEALDLSYNSQPFTMQGVGHNLSFVAQLPALRYLSLAHNDIHSRVSQQLCSASLC
ALDFSGNDLSRMWAEGDLYLRFFQGLRSLVWLDLSQNHLHTLLPRALDNLPKSLKHLHLRDNNLAFFNWSSLTLL
PKLETLDLAGNQLKALSNGSLPSGTQLRRLDLSGNSIGFVNPGFFALAKQLEELNLSANALKTVEPSWFGSMVGN
LKVLDVSANPLHCACGATFVGFLLEVQAAVPGLPSRVKCGSPGQLQGHSIFAQDLRLCLDETLSWNCFG

SEQ ID NO:7 (Porcine TLR9)

gagcacgaacatccttcactgtagctgctgcccggtctgccagccagacccctttggagaagaccccactccctgt
catgggcccccgctgcaccctgcaccccctttctctcctggtgcaggtgacagcgctggctgcggctctggccca
gggcaggctgcctgccttcctgccctgtgagctccagccccacggcctggtgaactgcaactggctcttcctgaa
gtccgtgccccacttctcggcggcagcgccccgggccaacgtcaccagcctctcctcttactctccaaccgcatcca
ccacctgcacgactccgacttcgtccacctgtccagcctacgaactctcaacctcaagtggaactgcccgccggc
tggcctcagccccatgcacttcccctgccacatgaccatcgagcccaacaccttcctggccgtgcccaccctgga
ggagctgaacctgagctacaacagcatcacgaccgtgcctgccctgcccgactccctcgtgtccctgtcgctgag
ccgcaccaacatcctggtgctagaccccacccacctcactggcctacatgccctgcgctacctgtacatggatgg
caactgctactacaagaacccctgccaggggcgctggaggtggtgccgggtgccctcctcggcctgggcaacct
cacacatctctcactcaagtacaacaatctcacggaggtgccccgcagcctgccccccagcctggagaccctgct
gttgtcctacaaccacattgtcaccctgacgcctgaggacctggccaatctgactgccctgcgcgtgcttgatgt
ggggggaactgccgccgctgtgaccatgcccgcaacccctgcagggagtgcccaaaggaccaccccaagctgca
ctctgacaccttcagccacctgagccgcctcgaaggcctggtgttgaaagacagttctctctacaacctggacac
caggtggttccgaggcctggacaggctccaagtgctggacctgagtgagaacttcctctacgactgcatcaccaa
gaccacggccttccagggcctggcccgactgcgcagcctcaacctgtccttcaattaccacaagaaggtgtcctt
tgcccacctgcacctggcaccctcctttgggcacctccggtccctgaaggagctggacatgcatggcatcttctt
ccgctcgctcagtgagaccacgctccaacctctggtccaactgcctatgctccagaccctgcgcctgcagatgaa
cttcattaaccaggcccagctcagcatctttggggccttccctggcctgctgtacgtggacctatcggacaaccg
catcagcggagctgcaaggccagtggccattactagggaggtggatggtagggagagggtctggctgccttccag
gaacctcgctccacgtccactggacactctccgctcagaggacttcatgccaaactgcaaggccttcagcttcac
cttggacctgtctcggaacaacctggtgacaatccagtcggagatgtttgctcgcctctcacgcctcgagtgcct
gcgcctgagccacaacagcatctcccaggcggtcaatggctctcagtttgtgccgctgaccagcctgcgggtgct
ggacctgtcccacaacaagctggacctgtatcacgggcgctcgttcacggagctgccgcgcctggaagcactgga
cctcagctacaatagccagccctttaccatgcagggtgtgggccacaacctcagcttcgtggcccagctgcccgc

cctgcgctacctcagcctggcgcacaatgacatccatagccgagtgtcccagcagctctgtagcgcctcactgtg
cgccctggactttagcggcaacgatctgagccggatgtgggctgagggagacctctatctccgcttcttccaagg
cctaagaagcctagtctggctggacctgtcccagaaccacctgcacaccctcctgccacgtgccctggacaacct
ccccaaaagcctgaagcatctgcatctccgtgacaataacctggccttcttcaactggagcagcctgaccctcct
gcccaagctggaaaccctggacttggctggaaaccagctgaaggccctaagcaatggcagcctgccatctggcac
ccagctgcggaggctggacctcagtggcaacagcatcggctttgtgaaccctggcttctttgccctggccaagca
gttagaagagctcaacctcagcgccaatgccctcaagacagtggagccctcctggtttggctcgatggtgggcaa
cctgaaagtcctagacgtgagcgccaaccctctgcactgtgcctgtggggcgaccttcgtgggcttcctgctgga
ggtacaggctgccgtgcctgggctgcccagccgcgtcaagtgtggcagtccggggcagctccagggccatagcat
ctttgcgcaagacctgcgcctctgcctggatgagaccctctcgtggaactgttttggcatctcgctgctggccat
ggccctgggcctggttgtgcccatgctgcaccacctctgcggctgggacctctggtactgcttccacctgtgcct
ggcctggctgccccaccgagggcagcggcggggcgcagacgccctgttctatgatgccttcgtggtctttgacaa
agctcagagtgctgtggccgactgggtgtacaacgagctgcgggtgcagctggaggagcgccgtgggcgccgcgc
actgcgcctgtgcctggaggagcgagactggttacctggcaagacgctcttcgagaacctgtgggcctcagtcta
cagcagccgcaagaccctgtttgtgctggcccacacggaccgtgtcagcggcctcttgcgtgccagtttcctgct
ggcccagcagcgcctgctggaggaccgcaaggacgttgtagtgctggtgatcctgcgccccgatgcctaccgctc
ccgctacgtgcggctgcgccagcgcctctgccgccagagtgtcctcctctggccccaccagccccgtgggcaggg
cagcttctgggcccagctgggcacagccctgaccagggacaaccaccacttctataaccggaacttctgccgggg
ccccacgacagccgaatagcactgagtgacagcccagttgccccagccccctggatttgcctctctgcctgggg
tgccccaacctgctttgctcagccacaccactgctctgctccctgttccccacccccacccccagcctggcatgt
aacatgtgcccaataaatgctaccggagggccaagaaaaaaaaaaaaaaaa

SEQ ID NO:8 (Porcine TLR9)

atgggcccccgctgcaccctgcacccccttttctctcctggtgcaggtgacagcgctggctgcggctctggcccag
ggcaggctgcctgccttcctgccctgtgagctccagccccacggcctggtgaactgcaactggctcttcctgaag
tccgtgccccacttctcggcggcagcgcccgggccaacgtcaccagcctctccttactctccaaccgcatccac
cacctgcacgactccgacttcgtccacctgtccagcctacgaactctcaacctcaagtggaactgcccgccggct
ggcctcagccccatgcacttcccctgccacatgaccatcgagcccaacaccttcctggccgtgcccaccctggag
gagctgaacctgagctacaacagcatcacgaccgtgcctgccctgcccgactccctcgtgtccctgtcgctgagc
cgcaccaacatcctggtgctagaccccacccacctcactggcctacatgccctgcgctacctgtacatggatggc
aactgctactacaagaacccctgccaggggcgctggaggtggtgccgggtgccctcctcggcctgggcaacctc
acacatctctcactcaagtacaacaatctcacggaggtgccccgcagcctgccccccagcctggagaccctgctg
ttgtcctacaaccacattgtcaccctgacgcctgaggacctggccaatctgactgccctgcgcgtgcttgatgtg
ggggggaactgccgccgctgtgaccatgcccgcaacccctgcagggagtgcccaaaggaccaccccaagctgcac
tctgacaccttcagccacctgagccgcctcgaaggcctggtgttgaaagacagttctctctacaacctggacacc
aggtggttccgaggcctggacaggctccaagtgctggacctgagtgagaacttcctctacgactgcatcaccaag
accacggccttccagggcctggcccgactgcgcagcctcaacctgtccttcaattaccacaagaaggtgtccttt
gcccacctgcacctggcaccctcctttgggcacctccggtccctgaaggagctggacatgcatggcatcttcttc
cgctcgctcagtgagaccacgctccaacctctggtccaactgcctatgctccagaccctgcgcctgcagatgaac
ttcattaaccaggcccagctcagcatctttggggccttccctggcctgctgtacgtggacctatcggacaaccgc
atcagcggagctgcaaggccagtggccattactagggaggtggatggtagggagagggtctggctgccttccagg
aacctcgctccacgtccactggacactctccgctcagaggacttcatgccaaactgcaaggccttcagcttcacc
ttggacctgtctcggaacaacctggtgacaatccagtcggagatgtttgctcgcctctcacgcctcgagtgcctg
cgcctgagccacaacagcatctcccaggcggtcaatggctctcagtttgtgccgctgaccagcctgcgggtgctg
gacctgtcccacaacaagctggacctgtatcacgggcgctcgttcacggagctgccgcgcctggaagcactggac
ctcagctacaatagccagccctttaccatgcagggtgtgggccacaacctcagcttcgtggcccagctgcccgcc
ctgcgctacctcagcctggcgcacaatgacatccatagccgagtgtcccagcagctctgtagcgcctcactgtgc
gccctggactttagcggcaacgatctgagccggatgtgggctgagggagacctctatctccgcttcttccaaggc
ctaagaagcctagtctggctggacctgtcccagaaccacctgcacaccctcctgccacgtgccctggacaacctc
cccaaaagcctgaagcatctgcatctccgtgacaataacctggccttcttcaactggagcagcctgaccctcctg
cccaagctggaaaccctggacttggctggaaaccagctgaaggccctaagcaatggcagcctgccatctggcacc
cagctgcggaggctggacctcagtggcaacagcatcggctttgtgaaccctggcttctttgccctggccaagcag
ttagaagagctcaacctcagcgccaatgccctcaagacagtggagccctcctggtttggctcgatggtgggcaac
ctgaaagtcctagacgtgagcgccaaccctctgcactgtgcctgtggggcgaccttcgtgggcttcctgctggag
gtacaggctgccgtgcctgggctgcccagccgcgtcaagtgtggcagtccggggcagctccagggccatagcatc
tttgcgcaagacctgcgcctctgcctggatgagaccctctcgtggaactgttttggc

SEQ ID NO:9 (Bovine TLR9)

MGPYCAPHPLSLLVQAAALAAALAEGTLPAFLPCELQPHGQVDCNWLFLKSVPHFSAGAPRANVTSLSLISNRIH
HLHDSDFVHLSNLRVLNLKWNCPPAGLSPMHFPCRMTIEPNTFLAVPTLEELNLSYNGITTVPALPSSLVSLSLS
HTSILVLGPTHFTGLHALRFLYMDGNCYYMNPCPRALEVAPGALLGLGNLTHLSLKYNNLTEVPRRLPPSLDTLL
LSYNHIVTLAPEDLANLTALRVLDVGGNCRRCDHARNPCRECPKNFPKLHPDTFSHLSRLEGLVLKDSSLYKLEK
DWFRGLGRLQVLDLSENFLYDYITKTTIFNDLTQLRRLNLSFNYHKKVSFAHLHLASSFGSLVSLEKLDMHGIFF
RSLTNITLQSLTRLPKLQSLHLQLNFINQAQLSIFGAFPSLLFVDLSDNRISGAATPAAALGEVDSRVEVWRLPR
GLAPGPLDAVSSKDFMPSCNLNFTLDLSRNNLVTIQQEMFTRLSRLQCLRLSHNSISQAVNGSQFVPLTSLRVLD
LSHNKLDLYHGRSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSASLRA
LDFSGNSLSQMWAEGDLYLCFFKGLRNLVQLDLSENHLHTLLPRHLDNLPKSLRQLRLRDNNLAFFNWSSLTVLP
RLEALDLAGNQLKALSNGSLPPGIRLQKLDVSSNSIGFVIPGFFVRATRLIELNLSANALKTVDPSWFGSLAGTL
KILDVSANPLHCACGAAFVDFLLERQEAVPGLSRRVTCGSPGQLQGRSIFTQDLRLCLDETLSLDCFGLSLLMVA
LGLAVPMLHHLCGWDLWYCFHLCLAHLPRRRRQRGEDTLLYDAVVVFDKVQSAVADWVYNELRVQLEERRGRRAL
RLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRLLEDRKDVVVLVILRPAAYRSR
YVRLRQRLCRQSVLLWPHQPSGQGSFWANLGIALTRDNRHFYNRNFCRGPTTAE

SEQ ID NO:10 (Bovine TLR9)

MGPYCAPHPLSLLVQAAALAAALAEGTLPAFLPCELQPHGQVDCNWLFLKSVPHFSAGAPRANVTSLSLISNRIH
HLHDSDFVHLSNLRVLNLKWNCPPAGLSPMHFPCRMTIEPNTFLAVPTLEELNLSYNGITTVPALPSSLVSLSLS
HTSILVLGPTHFTGLHALRFLYMDGNCYYMNPCPRALEVAPGALLGLGNLTHLSLKYNNLTEVPRRLPPSLDTLL
LSYNHIVTLAPEDLANLTALRVLDVGGNCRRCDHARNPCRECPKNFPKLHPDTFSHLSRLEGLVLKDSSLYKLEK
DWFRGLGRLQVLDLSENFLYDYITKTTIFNDLTQLRRLNLSFNYHKKVSFAHLHLASSFGSLVSLEKLDMHGIFF
RSLTNITLQSLTRLPKLQSLHLQLNFINQAQLSIFGAFPSLLFVDLSDNRISGAATPAAALGEVDSRVEVWRLPR
GLAPGPLDAVSSKDFMPSCNLNFTLDLSRNNLVTIQQEMFTRLSRLQCLRLSHNSISQAVNGSQFVPLTSLRVLD
LSHNKLDLYHGRSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSASLRA
LDFSGNSLSQMWAEGDLYLCFFKGLRNLVQLDLSENHLHTLLPRHLDNLPKSLRQLRLRDNNLAFFNWSSLTVLP
RLEALDLAGNQLKALSNGSLPPGIRLQKLDVSSNSIGFVIPGFFVRATRLIELNLSANALKTVDPSWFGSLAGTL
KILDVSANPLHCACGAAFVDFLLERQEAVPGLSRRVTCGSPGQLQGRSIFTQDLRLCLDETLSLDCFG

SEQ ID NO:11 (Bovine TLR9)

gggaagtgggcgccaagcatccttccctgcagctgcctcccaacctgcccgccagaccctctggagaagccgcat
tccctgtcatgggcccctactgtgccccgcacccccttttctctcctggtgcaggcggcggcactggcagcggccc
tggccgagggcaccctgcctgccttcctgccctgtgagctccagccccatggtcaggtggactgcaactggctgt
tcctgaagtctgtgccgcacttttcggctggagccccccgggccaatgtcaccagcctctccttaatctccaacc
gcatccaccacttgcatgactctgacttcgtccacctgtccaacctgcgggtcctcaacctcaagtggaactgcc
cgccggccggcctcagccccatgcacttcccctgccgtatgaccatcgagcccaacaccttcctggctgtgccca
ccctggaggagctgaacctgagctacaacggcatcacgaccgtgcctgccctgcccagttccctcgtgtccctgt
cgctgagccacaccagcatcctggtgctaggccccacccacttcaccggcctgcacgccctgcgctttctgtaca
tggacggcaactgctactacatgaacccctgcccgcgggccctggaggtggccccaggcgccctcctcggcctgg
gcaacctcacgcacctgtcgctcaagtacaacaacctcacggaggtgccccgccgcctgccccccagcctggaca
ccctgctgctgtcctacaaccacattgtcaccctggcacccgaggacctggccaacctgactgccctgcgcgtgc
ttgacgtgggtgggaactgccgccgctgcgaccatgcccgcaacccctgcagggagtgcccaaagaacttcccca
agctgcaccctgacaccttcagtcacctgagccgcctcgaaggcctggtgttgaaggacagttctctctacaaac
tagagaaagattggttccgcggcctgggcaggctccaagtgctcgacctgagtgagaacttcctctatgactaca
tcaccaagaccaccatcttcaacgacctgacccagctgcgcagactcaacctgtccttcaattaccacaagaagg
tgtccttcgcccacctgcacctagcgtcctcctttgggagtctggtgtccctggagaagctggacatgcacggca
tcttcttccgctccctcaccaacatcacgctccagtcgctgacccggctgcccaagctccagagtctgcatctgc
agctgaacttcatcaaccaggcccagctcagcatctttggggccttcccgagcctgctcttcgtggacctgtcgg
acaaccgcatcagcggagccgcgacgccagcggccgccctgggggaggtggacagcagggtggaagtctggcgat
tgcccaggggcctcgctccaggcccgctggacgccgtcagctcaaaggacttcatgccaagctgcaacctcaact
tcaccttggacctgtcacggaacaacctggtgacaatccagcaagagatgtttacccgcctctcccgcctccagt
gcctgcgcctgagccacaacagcatctcgcaggcggttaatggctcccagttcgtgccgctgaccagcctgcgag

tgctcgacctgtcccacaacaagctggacctgtaccatgggcgctcattcacggagctgccgcagctggaggcac
tggacctcagctacaacagccagcccttcagcatgcagggcgtgggccacaacctcagcttcgtggcccagctgc
cctccctgcgctacctcagccttgcgcacaatggcatccacagccgcgtgtcacagaagctcagcagcgcctcgt
tgcgcgccctggacttcagcggcaactccctgagccagatgtgggccgagggagacctctatctctgctttttca
aaggcttgaggaacctggtccagctggacctgtccgagaaccatctgcacaccctcctgcctcgtcacctggaca
acctgcccaagagcctgcggcagctgcgtctccgggacaataacctggccttcttcaactggagcagcctgaccg
tcctgccccggctggaagccctggatctggcaggaaaccagctgaaggccctgagcaacggcagcctgccgcctg
gcatccggctccagaagctggacgtgagcagcaacagcatcggcttcgtgatccccggcttcttcgtccgcgcga
ctcggctgatagagcttaacctcagcgccaatgccctgaagacagtggatccctcctggttcggttccttagcag
ggaccctgaaaatcctagacgtgagcgccaacccgctccactgcgcctgcggggcggcctttgtggacttcctgc
tggagagacaggaggccgtgcccgggctgtccaggcgcgtcacatgtggcagtccgggccagctccagggccgca
gcatcttcacacaggacctgcgcctctgcctggatgagaccctctccttggactgctttggcctctcactgctaa
tggtggcgctgggcctggcagtgcccatgctgcaccacctctgtggctgggacctctggtactgcttccacctgt
gtctggcccatttgccccgacggcggcggcagcggggcgaggacaccctgctctatgatgccgtcgtggtcttcg
acaaggtgcagagtgcagtggctgattgggtgtacaacgagctccgcgtgcagctggaggagcgccgggggcgcc
gggcgctccgcctctgcctggaggagcgagactggctccctggtaagacgctcttcgagaacctgtgggcctcgg
tctacagcagccgcaagaccatgttcgtgctggaccacacggaccgggtcagcggcctcctgcgccgccagcttcc
tgctggcccagcagcgcctgttggaggaccgcaaggacgtcgtagtgctggtgatcctgcgcccgccgcctatc
ggtcccgctacgtgcggctgcgccagcgcctctgccgccagagcgtcctcctctggccccaccagcccagtggcc
agggtagtttctgggccaacctgggcatagccctgaccagggacaaccgtcacttctataaccggaacttctgcc
ggggccccacgacagccgaatagcacagagtgactgcccag

SEQ ID NO:12 (Bovine TLR9)

atgggcccctactgtgccccgcacccccttttctctcctggtgcaggcggcggcactggcagcggccctggccgag
ggcaccctgcctgccttcctgccctgtgagctccagccccatggtcaggtggactgcaactggctgttcctgaag
tctgtgccgcacttttcggctggagcccccgggccaatgtcaccagcctctccttaatctccaaccgcatccac
cacttgcatgactctgacttcgtccacctgtccaacctgcgggtcctcaacctcaagtggaactgcccgccggcc
ggcctcagccccatgcacttcccctgccgtatgaccatcgagcccaacacctttcctggctgtgcccaccctggag
gagctgaacctgagctacaacggcatcacgaccgtgcctgccctgcccagttccctcgtgtccctgtcgctgagc
cacaccagcatcctggtgctaggccccacccacttcaccggcctgcacgccctgcgctttctgtacatggacggc
aactgctactacatgaacccctgcccgcgggccctggaggtggccccaggcgccctcctcggcctgggcaacctc
acgcacctgtcgctcaagtacaacaacctcacggaggtgccccgccgcctgccccccagcctggacaccctgctg
ctgtcctacaaccacattgtcaccctggcacccgaggacctggccaacctgactgccctgcgcgtgcttgacgtg
ggtgggaactgccgccgctgcgaccatgcccgcaacccctgcagggagtgcccaaagaacttccccaagctgcac
cctgacaccttcagtcacctgagccgcctcgaaggcctggtgttgaaggacagttctctctacaaactagagaaa
gattggttccgcggcctgggcaggctccaagtgctcgacctgagtgagaacttcctctatgactacatcaccaag
accaccatcttcaacgacctgacccagctgcgcagactcaacctgtccttcaattaccacaagaaggtgtccttc
gcccacctgcacctagcgtcctcctttgggagtctggtgtccctggagaagctggacatgcacggcatcttcttc
cgctccctcaccaacatcacgctccagtcgctgacccggctgcccaagctccagagtctgcatctgcagctgaac
ttcatcaaccaggcccagctcagcatctttggggccttcccgagcctgctcttcgtggacctgtcggacaaccgc
atcagcggagccgcgacgccagcggccgccctgggggaggtggacagcagggtggaagtctggcgattgcccagg
ggcctcgctccaggcccgctggacgccgtcagctcaaaggacttcatgccaagctgcaacctcaacttcaccttg
gacctgtcacggaacaacctggtgacaatccagcaagagatgtttacccgcctctcccgcctccagtgcctgcgc
ctgagccacaacagcatctcgcaggcggttaatggctcccagttcgtgccgctgaccagcctgcgagtgctcgac
ctgtcccacaacaagctggacctgtaccatgggcgctcattcacggagctgccgcagctggaggcactggacctc
agctacaacagccagcccttcagcatgcagggcgtgggccacaacctcagcttcgtggcccagctgccctccctg
cgctacctcagccttgcgcacaatggcatccacagccgcgtgtcacagaagctcagcagcgcctcgttgcgcgcc
ctggacttcagcggcaactccctgagccagatgtgggccgagggagacctctatctctgctttttcaaaggcttg
aggaacctggtccagctggacctgtccgagaaccatctgcacaccctcctgcctcgtcacctggacaacctgccc
aagagcctgcggcagctgcgtctccgggacaataacctggccttcttcaactggagcagcctgaccgtcctgccc
cggctggaagccctggatctggcaggaaaccagctgaaggccctgagcaacggcagcctgccgcctggcatccgg
ctccagaagctggacgtgagcagcaacagcatcggcttcgtgatccccggcttcttcgtccgcgcgactcggctg
atagagcttaacctcagcgccaatgccctgaagacagtggatccctcctggttcggttccttagcagggaccctg
aaaatcctagacgtgagcgccaacccgctccactgcgcctgcggggcggcctttgtggacttcctgctggagaga
caggaggccgtgcccgggctgtccaggcgcgtcacatgtggcagtccgggccagctccagggccgcagcatcttc
acacaggacctgcgcctctgcctggatgagaccctctccttggactgctttggc

SEQ ID NO:13 (Equine TLR9)

MGPCHGALQPLSLLVQAAMLAVALAQGTLPPFLPCELQPHGLVNCNWLFLKSVPHFSAAAPRDNVTSLSLLSNRI
HHLHDSDFAQLSNLQKLNLKWNCPPAGLSPMHFPCHMTIEPNTFLAVPTLEELNLSYNGITTVPALPSSLVSLIL
SRTNILQLDPTSLTGLHALRFLYMDGNCYYKNPCGRALEVAPGALLGLGNLTHLSLKYNNLTTVPRSLPPSLEYL
LLSYNHIVTLAPEDLANLTALRVLDVGGNCRRCDHARNPCVECPHKFPQLHSDTFSHLSRLEGLVLKDSSLYQLN
PRWFRGLGNLTVLDLSENFLYDCITKTKAFQGLAQLRRLNLSFNYHKKVSFAHLTLAPSFGSLLSLQELDMHGIF
FRSLSQKTLQPLARLPMLQRLYLQMNFINQAQLGIFKDFPGLRYIDLSDNRISGAVEPVATTGEVDGGKKVWLTS
RDLTPGPLDTPSSEDFMPSCKNLSFTLDLSRNNLVTVQPEMFAQLSRLQCLRLSHNSISQAVNGSQFVPLTSLQV
LDLSHNKLDLYHGRSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCSTSL
WALDFSGNSLSQMWAEGDLYLRFFQGLRSLIRLDLSQNRLHTLLPCTLGNLPKSLQLLRLRNNYLAFFNWSSLTL
LPNLETLDLAGNQLKALSNGSLPSGTQLQRLDVSRNSIIFVVPGFFALATRLRELNLSANALRTEEPSWFGFLAG
SLEVLDVSANPLHCACGAAFVDFLLQVQAAVPGLPSRVKCGSPGQLQGRSIFAQDLRLCLDKSLSWDCFGLSLLV
VALGLAMPMLHHLCGWDLWYCFHLGLAWLPRRGWQRGADALSYDAFVVFDKAQSAVADWVYNELRVRLEERRGRR
ALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDQVSGLLRASFLLAQQRLLEDRKDVVVLVILSPDARR
SRYVRLRQRLCRQSVLFWPHQPSGQRSFWAQLGMALTRDNRHFYNQNFCRGPTMAE

SEQ ID NO:14 (Equine TLR9)

MGPCHGALQPLSLLVQAAMLAVALAQGTLPPFLPCELQPHGLVNCNWLFLKSVPHFSAAAPRDNVTSLSLLSNRI
HHLHDSDFAQLSNLQKLNLKWNCPPAGLSPMHFPCHMTIEPNTFLAVPTLEELNLSYNGITTVPALPSSLVSLIL
SRTNILQLDPTSLTGLHALRFLYMDGNCYYKNPCGRALEVAPGALLGLGNLTHLSLKYNNLTTVPRSLPPSLEYL
LLSYNHIVTLAPEDLANLTALRVLDVGGNCRRCDHARNPCVECPHKFPQLHSDTFSHLSRLEGLVLKDSSLYQLN
PRWFRGLGNLTVLDLSENFLYDCITKTKAFQGLAQLRRLNLSFNYHKKVSFAHLTLAPSFGSLLSLQELDMHGIF
FRSLSQKTLQPLARLPMLQRLYLQMNFINQAQLGIFKDFPGLRYIDLSDNRISGAVEPVATTGEVDGGKKVWLTS
RDLTPGPLDTPSSEDFMPSCKNLSFTLDLSRNNLVTVQPEMFAQLSRLQCLRLSHNSISQAVNGSQFVPLTSLQV
LDLSHNKLDLYHGRSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCSTSL
WALDFSGNSLSQMWAEGDLYLRFFQGLRSLIRLDLSQNRLHTLLPCTLGNLPKSLQLLRLRNNYLAFFNWSSLTL
LPNLETLDLAGNQLKALSNGSLPSGTQLQRLDVSRNSIIFVVPGFFALATRLRELNLSANALRTEEPSWFGFLAG
SLEVLDVSANPLHCACGAAFVDFLLQVQAAVPGLPSRVKCGSPGQLQGRSIFAQDLRLCLDKSLSWDCFG

SEQ ID NO:15 (Equine TLR9)

ctctgttctctgagctgttgccgcgtgaagggactgcgagcacaaagcatcctcctctgcagctgctgcccagtg
tgccagctggaccctctggatcatctcccactccctgtcatgggcccttgccatggtgccctgcagcccctgtct
ctcctggtgcaggcggccatgctggccgtggctctggcccaaggcaccctgcctcccttcctgccctgtgagctc
cagccccacggcctggtgaactgcaactggctgttcctgaagtccgtgccccacttctcagcagcagcaccccgg
gacaatgtcaccagcctttccttgctctccaaccgcatccaccacctccacgactccgactttgcccaactgtcc
aacctgcagaaactcaacctcaaatggaactgcccgccagccggcctcagccccatgcacttcccctgccacatg
accatcgagcccaacactttcctggctgtacccaccctggaggagctgaacctgagctacaacggcatcacgact
gtgcctgccctgcccagctccctcgtgtccctgatcctgagccgcaccaacatcctgcagctagaccccaccagc
ctcacgggcctgcatgccctgcgcttcctatacatggatggcaactgctactacaagaacccctgcgggcgggcc
ctggaggtggccccaggcgccctccttggcctgggcaacctcacccacctgtcactcaagtacaacaacctcaca
acggtgccccgcagcctgccccctagcctggagtacctgctgttgtcctacaaccacattgtcaccctggcacct
gaggacctggccaatctgactgccctgcgtgtgctcgatgtgggtggaaactgccgccgctgtgaccatgcacgc
aacccctgcgtggagtgcccacataaattcccccagctgcactccgacaccttcagccacctaagccgcctagaa
ggcctcgtgttgaaggatagttctctctaccagctgaaccccagatggttccgtggcctgggcaacctcacagtg
ctcgacctgagtgagaacttcctctacgactgcatcaccaaaaccaaggcattccagggcctggcccagctgcga
agactcaacttgtccttcaattaccataagaaggtgtccttcgcccacctgacgctggcaccctccttcgggagc
ctgctctccctgcaggaactggacatgcatggcatcttcttccgctcactcagccagaagacgctccagccactg
gcccgcctgcccatgctccagcgtctgtatctgcagatgaacttcatcaaccaggcccagctcggcatcttcaag
gacttccctggtctgcgctacatagacctgtcagacaaccgcatcagtggagctgtggagccggtggccaccaca
ggggaggtggatggtgggaagaaggtctggctgacatccagggacctcactccaggcccactggacacccccagc
tctgaggacttcatgccaagctgcaagaacctcagcttcaccttggacctgtcacggaacaacctggtaacagtc
cagccagagatgtttgcccagctctcgcgcctccagtgcctgcgcctgagccacaacagcatctcgcaggcggtc

aatggctcacagttcgtgccactgaccagcctgcaggtgctggacctgtcccataacaaactggacctgtaccat
gggcgctcgtttacggagctgccgcgactggaggccctggacctcagctacaacagccagcccttcagcatgcgg
ggtgtgggccacaacctcagctttgtggcccagctgcccaccctgcgctacctcagcctggcacacaatggcatc
cacagccgtgtgtcccagcagctctgcagcacctcgctgtgggccctggacttcagcggcaattccctgagccag
atgtgggctgagggagacctctatctccgcttcttccaaggcctgagaagcctaatccggctagacctgtcccag
aatcgtctgcataccctcctgccatgcaccctgggcaacctccccaagagcttgcagctgctgcgtctccgtaac
aattacctggccttcttcaattggagcagcctgaccctcctgcccaacctggaaaccctggacctggctggaaac
cagctgaaggctctgagcaatggcagcctgccttctggcacccagctccagaggctggacgtcagcaggaacagc
atcatcttcgtggtccctggcttctttgctctggccacgaggctgcgagagctcaacctcagtgccaacgccctc
aggacagaggagccctcctggtttggtttcctagcaggctcccttgaagtcctagatgtgagcgccaaccctctg
cactgcgcctgtggggcagcctttgtggacttcctgctgcaggttcaggctgccgtgcctggtctgcccagccgc
gtcaagtgtggcagtccgggccagctccagggccgcagcatcttcgcacaagacctgcgcctctgcctggacaag
tccctctcctgggactgttttggtctctcattgctggttgtggccctgggcctggccatgcctatgttgcaccac
ctctgcggctgggacctctggtactgcttccacctgggcctggcctggctgcccggcgggggtggcagcggggc
gcggatgccctgagctatgatgcctttgtggtcttcgacaaggcacagagcgcagtggccgactgggtgtacaat
gaactgcgggtgcggctagaggagcgccgtgggcgccgggcgctccgcctgtgtctggaggagcgtgactggcta
cctggcaagacgctgttcgaaaacctgtgggcctcagtctacagcagccgcaagatgctgtttgtgctggcccac
acggaccaggtcagtggcctcttgcgtgccagcttcctgctggcccagcagcgtctgctggaggaccgcaaggac
gttgtggtgctggtaatcctgagccctgacgcccgccgttcccgttacgtgcggctgcgccagcgcctctgccgc
cagagtgtcctcttctggccccaccagcctagtggccagcgcagcttctgggcccagctaggcatggccctgacc
agggacaaccgccacttctataaccagaacttctgccggggcccgacgatggctgagtagcacagagtgacagcc
tggcatgtacaacccccagccctgaccttgcctctctgcctatgatgcccagtctgcctcactctgtgacgcccc
tgctctgcctccgccaccctcacccctggcatacagcaggcactcaataaatgccactggcaggccaaacagcca
aaaaaaaaaaaaaaa

SEQ ID NO:16 (Equine TLR9)

atgggcccttgccatggtgccctgcagcccctgtctctcctggtgcaggcggccatgctggccgtggctctggcc
caaggcaccctgcctcccttcctgccctgtgagctccagccccacggcctggtgaactgcaactggctgttcctg
aagtccgtgccccacttctcagcagcagcaccccgggacaatgtcaccagcctttccttgctctccaaccgcatc
caccacctccacgactccgactttgcccaactgtccaacctgcagaaactcaacctcaaatggaactgcccgcca
gccggcctcagccccatgcacttcccctgccacatgaccatcgagcccaacactttcctggctgtacccaccctg
gaggagctgaacctgagctacaacggcatcacgactgtgcctgccctgcccagctccctcgtgtccctgatcctg
agccgcaccaacatcctgcagctagaccccaccagcctcacgggcctgcatgccctgcgcttcctatacatggat
ggcaactgctactacaagaaccctgcgggcgggccctggaggtggccccaggcgccctccttggcctgggcaac
ctcacccacctgtcactcaagtacaacaacctcacaacggtgccccgcagcctgccccctagcctggagtacctg
ctgttgtcctacaaccacattgtcaccctggcacctgaggacctggccaatctgactgccctgcgtgtgctcgat
gtgggtggaaactgccgccgctgtgaccatgcacgcaacccctgcgtggagtgcccacataaattcccccagctg
cactccgacaccttcagccacctaagccgcctagaaggcctcgtgttgaaggatagttctctctaccagctgaac
cccagatggttccgtggcctgggcaacctcacagtgctcgacctgagtgagaacttcctctacgactgcatcacc
aaaaccaaggcattccagggcctggcccagctgcgaagactcaacttgtccttcaattaccataagaaggtgtcc
ttcgcccacctgacgctggcaccctccttcgggagcctgctctccctgcaggaactggacatgcatggcatcttc
ttccgctcactcagccagaagacgctccagccactggcccgcctgcccatgctccagcgtctgtatctgcagatg
aacttcatcaaccaggcccagctcggcatcttcaaggacttccctggtctgcgctacatagacctgtcagacaac
cgcatcagtggagctgtggagccggtggccaccacaggggaggtggatggtgggaagaaggtctggctgacatcc
agggacctcactccaggcccactggacacccccagctctgaggacttcatgccaagctgcaagaacctcagcttc
accttggacctgtcacggaacaacctggtaacagtccagccagagatgtttgcccagctctcgcgcctccagtgc
ctgcgcctgagccacaacagcatctcgcaggcggtcaatggctcacagttcgtgccactgaccagcctgcaggtg
ctggacctgtcccataacaaactggacctgtaccatgggcgctcgtttacggagctgccgcgactggaggccctg
gacctcagctacaacagccagcccttcagcatgcggggtgtgggccacaacctcagctttgtggcccagctgccc
accctgcgctacctcagcctggcacacaatggcatccacagccgtgtgtcccagcagctctgcagcacctcgctg
tgggccctggacttcagcggcaattccctgagccagatgtgggctgagggagacctctatctccgcttcttccaa
ggcctgagaagcctaatccggctagacctgtcccagaatcgtctgcataccctcctgccatgcaccctgggcaac
ctccccaagagcttgcagctgctgcgtctccgtaacaattacctggccttcttcaattggagcagcctgaccctc
ctgcccaacctggaaaccctggacctggctggaaaccagctgaaggctctgagcaatggcagcctgccttctggc
acccagctccagaggctggacgtcagcaggaacagcatcatcttcgtggtccctggcttctttgctctggccacg
aggctgcgagagctcaacctcagtgccaacgccctcaggacagaggagccctcctggtttggtttcctagcaggc
tcccttgaagtcctagatgtgagcgccaaccctctgcactgcgcctgtggggcagcctttgtggacttcctgctg

caggttcaggctgccgtgcctggtctgcccagccgcgtcaagtgtggcagtccgggccagctccagggccgcagc
atcttcgcacaagacctgcgcctctgcctggacaagtccctctcctgggactgttttggt

SEQ ID NO:17 (Ovine TLR9)

MGPYCAPHPLSLLVQAAALAAALAQGTLPAFLPCELQPRGKVNCNWLFLKSVPRFSAGAPRANVTSLSLISNRIH
HLHDSDFVHLSNLRVLNLKWNCPPAGLSPMHFPCRMTIEPNTFLAVPTLEELNLSYNGITTVPALPSSLVSLSLS
RTSILVLGPTHFTGLHALRFLYMDGNCYYKNPCQQAVEVAPGALLGLGNLTHLSLKYNNLTEVPRRLPPSLDTLL
LSYNHIITLAPEDLANLTALRVLDVGGNCRRCDHARNPCRECPKNFPKLHPDTFSHLSRLEGLVLKDSSLYKLEK
DWFRGLGRLQVLDLSENFLYDYITKTTIFRNLTQLRRLNLSFNYHKKVSFAHLQLAPSFGGLVSLEKLDMHGIFF
RSLTNTTLRPLTQLPKLQSLSLQLNFINQAELSIFGAFPSLLFVDLSDNRISGAARPVAALGEVDSGVEVWRWPR
GLAPGPLAAVSAKDFMPSCNLNFTLDLSRNNLVTIQQEMFTRLSRLQCLRLSHNSISQAVNGSQFVPLTRLRVLD
LSYNKLDLYHGRSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSASLRA
LDFSGNSLSQMWAEGDLYLCFFKGLRNLVQLDLSKNHLHTLLPRHLDNLPKSLRQLRLRDNNLAFFNWSSLTVLP
QLEALDLAGNQLKALSNGSLPPGTRLQKLDVSSNSIGFVTPGFFVLANRLKELNLSANALKTVDPFWFGRLTETL
NILDVSANPLHCACGAAFVDFLLEMQAAVPGLSRRVTCGSPGQLQGRSIFAQDLRLCLDETLSLDCFGFSLLMVA
LGLAVPMLHHLCGWDLWYCFHLCLAHLPRRRRQRGEDTLLYDAFVVFDKAQSAVADWVYNELRVQLEERRGRRAL
RLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRLLEDRKDVVVLVILRPAAYRSR
YVRLRQRLCRQSVLLWPHQPSGQGSFWANLGMALTRDNRHFYNRNFCRGPTTAE

SEQ ID NO:18 (Ovine TLR9)

MGPYCAPHPLSLLVQAAALAAALAQGTLPAFLPCELQPRGKVNCNWLFLKSVPRFSAGAPRANVTSLSLISNRIH
HLHDSDFVHLSNLRVLNLKWNCPPAGLSPMHFPCRMTIEPNTFLAVPTLEELNLSYNGITTVPALPSSLVSLSLS
RTSILVLGPTHFTGLHALRFLYMDGNCYYKNPCQQAVEVAPGALLGLGNLTHLSLKYNNLTEVPRRLPPSLDTLL
LSYNHIITLAPEDLANLTALRVLDVGGNCRRCDHARNPCRECPKNFPKLHPDTFSHLSRLEGLVLKDSSLYKLEK
DWFRGLGRLQVLDLSENFLYDYITKTTIFRNLTQLRRLNLSFNYHKKVSFAHLQLAPSFGGLVSLEKLDMHGIFF
RSLTNTTLRPLTQLPKLQSLSLQLNFINQAELSIFGAFPSLLFVDLSDNRISGAARPVAALGEVDSGVEVWRWPR
GLAPGPLAAVSAKDFMPSCNLNFTLDLSRNNLVTIQQEMFTRLSRLQCLRLSHNSISQAVNGSQFVPLTRLRVLD
LSYNKLDLYHGRSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSASLRA
LDFSGNSLSQMWAEGDLYLCFFKGLRNLVQLDLSKNHLHTLLPRHLDNLPKSLRQLRLRDNNLAFFNWSSLTVLP
QLEALDLAGNQLKALSNGSLPPGTRLQKLDVSSNSIGFVTPGFFVLANRLKELNLSANALKTVDPFWFGRLTETL
NILDVSANPLHCACGAAFVDFLLEMQAAVPGLSRRVTCGSPGQLQGRSIFAQDLRLCLDETLSLDCFG

SEQ ID NO:19 (Ovine TLR9)

gtcggcacgggaagtgagcgccaagcatccttccctgcagctgccgcccaacttgcccgccagaccctctggaga
agccgcattccctgccatgggcccctactgtgccccgcacccccttttctctcctggtgcaggcggcggcgctggc
agcagccctggcccagggcaccctgcctgccttcctgccctgtgagctccagccccggggtaaggtgaactgcaa
ctggctgttcctgaagtctgtgccgcgcttttcggccggagccccccgggccaatgtcaccagcctctccttaat
ctccaaccgcatccaccacttgcacgactctgacttcgtccacctgtccaacctgcgggtcctcaacctcaagtg
gaactgcccgccggccggcctcagccccatgcacttcccctgccgcatgaccatcgagcccaacaccttcctggc
tgtgcccaccctggaggagctgaacctgagctacaatggcatcacgaccgtgcctgccctgcccagttctctcgt
atccctgtcgctgagccgcaccagcatcctggtgctaggccccacccacttcaccggcctgcacgccctgcgctt
tctgtacatggacggcaactgctactataagaacccctgccagcaggccgtggaggtggccccaggcgccctcct
tggcctgggcaacctcacgcacctgtcgctcaagtacaacaacctcacggaggtgccccgccgcctgccccccag
cctggacaccctgctgctgtcctacaaccacatcatcaccctggcacccgaggacctggccaatctgactgccct
gcgtgtgcttgatgtgggcgggaactgccgccgctgcgaccacgcccgcaaccccctgcagggagtgcccaaagaa
cttccccaagctgcaccctgacaccttcagccacctgagccgcctcgaaggcctggtgttgaaggacagttctct
ctacaaactagagaaagactggttccgcggcctgggcaggctccaagtgctcgacctgagtgagaacttcctcta
tgactacatcaccaagaccaccatcttcaggaacctgacccagctgcgcagactcaacctgtccttcaattacca
caagaaggtgtccttcgcccacctgcaactggcaccctcctttgggggcctggtgtccctggagaagctggacat
gcacggcatcttcttccgctccctcaccaacaccacgctccggccgctgacccagctgcccaagctccagagtct
gagtctgcagctgaacttcatcaaccaggccgagctcagcatctttggggccttcccgagcctgctcttcgtgga
cctgtcggacaaccgcatcagcggagctgcgaggccggtggccgcctcggggaggtggacagcggggtggaagt
ctggcggtggcccaggggcctcgctccaggcccgctggccgccgtcagcgcaaaggacttcatgccaagctgcaa

cctcaacttcaccttggacctgtcacggaacaacctggtgacgatccagcaggagatgtttacccgcctctcccg
cctccagtgcctgcgcctgagccacaacagcatctcgcaggcggttaatggctcgcagttcgtgccgctgacccg
cctgcgagtgctcgacctgtcctacaacaagctggacctgtaccatgggcgctcgttcacggagctgccgcagct
ggaggcactggacctcagctacaacagccagcccttcagcatgcagggcgtgggccacaacctcagcttcgtggc
ccagctgccgtccctgcgctacctcagccttgcgcacaacggcatccacagccgcgtgtcacagaagctcagcag
cgcctcgctgcgcgccctggacttcagcggcaactccctgagccagatgtgggccgagggagacctctatctctg
cttcttcaaaggcttgaggaacctggtccagctggacctgtccaagaaccacctgcacaccctcctgcctcgtca
cctggataacctgcccaagagcctgcggcagctgcgtctccgggacaataacctggccttcttcaactggagcag
cctgactgttctgccccagctggaagccctggatctggcgggaaaccagctgaaggccctgagcaacggcagcct
gccacctggcacccggctccagaagctggacgtgagcagcaacagcatcggctttgtgacccctggcttctttgt
ccttgccaaccggctgaaagagcttaacctcagcgccaacgccctgaagacagtggatcccttctggttcggtcg
cttaacagagaccctgaatatcctagacgtgagcgccaacccgctccactgtgcctgcggggcggcctttgtgga
cttcctgctggagatgcaggcggccgtgcctgggctgtccaggcgcgtcacgtgtggcagtccgggccagctcca
gggccgcagcatcttcgcacaggacctgcgcctctgcctggatgagaccctctccttggactgctttggcttctc
gctgctaatggtggcgctgggcctggcggtgcccatgctgcaccacctctgtggctgggacctgtggtactgctt
ccacctgtgtctggcccatttgccccgacggcggcggcagcggggcgaggacaccctgctctacgatgccttcgt
ggtcttcgacaaggcgcagagtgcagtggccgactgggtgtacaacgagctccgcgtgcagctggaggagcgccg
cgggcgccgggcgctccgcctctgcctggaggagcgagactggctccctggcaagacgctcttcgagaacctgtg
ggcctcggtctacagcagccgtaagaccatgttcgtgctggaccacacggaccgggtcagtggcctcctgcgcgc
cagcttcctgctggcccagcagcgcctgttggaggaccgcaaggatgtcgtggtgctggtgatcctgcgccccgc
cgcctaccggtcccgctacgtgcggctgcgccagcgcctctgccgccagagcgtcctcctctggccccaccagcc
cagtggccagggtagcttctgggccaacctgggcatggccctgaccagggacaaccgccacttctataaccggaa
cttctgccggggccccacgacagccgaatagcacagagtgactgcccag

SEQ ID NO:20 (Ovine TLR9)

atgggcccctactgtgccccgcacccccttttctctcctggtgcaggcggcggcgctggcagcagccctggcccag
ggcaccctgcctgccttcctgccctgtgagctccagccccggggtaaggtgaactgcaactggctgttcctgaag
tctgtgccgcgctttcggccggagccccccgggccaatgtcaccagcctctccttaatctccaaccgcatccac
cacttgcacgactctgacttcgtccacctgtccaacctgcgggtcctcaacctcaagtggaactgcccgccggcc
ggcctcagccccatgcacttcccctgccgcatgaccatcgagcccaacaccttcctggctgtgcccaccctggag
gagctgaacctgagctacaatggcatcacgaccgtgcctgccctgcccagttctctcgtatccctgtcgctgagc
cgcaccagcatcctggtgctaggccccacccacttcaccggcctgcacgccctgcgctttctgtacatggacggc
aactgctactataagaacccctgccagcaggccgtggaggtggccccaggcgccctccttggcctgggcaacctc
acgcacctgtcgctcaagtacaacaacctcacggaggtgccccgccgcctgccccccagcctggacaccctgctg
ctgtcctacaaccacatcatcaccctggcacccgaggacctggccaatctgactgccctgcgtgtgcttgatgtg
ggcgggaactgccgccgctgcgaccacgcccgcaacccctgcagggagtgcccaaagaacttccccaagctgcac
cctgacaccttcagccacctgagccgcctcgaaggcctggtgttgaaggacagttctctctacaaactagagaaa
gactggttccgcggcctgggcaggctccaagtgctcgacctgagtgagaacttcctctatgactacatcaccaag
accaccatcttcaggaacctgacccagctgcgcagactcaacctgtccttcaattaccacaagaaggtgtccttc
gcccacctgcaactggcaccctcctttgggggcctggtgtccctggagaagctggacatgcacggcatcttcttc
cgctccctcaccaacaccacgctccggccgctgacccagctgcccaagctccagagtctgagtctgcagctgaac
ttcatcaaccaggccgagctcagcatctttggggccttcccgagcctgctcttcgtggacctgtcggacaaccgc
atcagcggagctgcgaggccggtggccgccctcggggaggtggacagcggggtggaagtctggcggtggcccagg
ggcctcgctccaggcccgctggccgccgtcagcgcaaaggacttcatgccaagctgcaacctcaacttcaccttg
gacctgtcacggaacaacctggtgacgatccagcaggagatgtttacccgcctctcccgcctccagtgcctgcgc
ctgagccacaacagcatctcgcaggcggttaatggctcgcagttcgtgccgctgacccgcctgcgagtgctcgac
ctgtcctacaacaagctggacctgtaccatgggcgctcgttcacggagctgccgcagctggaggcactggacctc
agctacaacagccagcccttcagcatgcagggcgtgggccacaacctcagcttcgtggcccagctgccgtccctg
cgctacctcagccttgcgcacaacggcatccacagccgcgtgtcacagaagctcagcagcgcctcgctgcgcgcc
ctggacttcagcggcaactccctgagccagatgtgggccgagggagacctctatctctgcttcttcaaaggcttg
aggaacctggtccagctggacctgtccaagaaccacctgcacaccctcctgcctcgtcacctggataacctgccc
aagagcctgcggcagctgcgtctccgggacaataacctggccttcttcaactggagcagcctgactgttctgccc
cagctggaagccctggatctggcgggaaaccagctgaaggccctgagcaacggcagcctgccacctggcacccgg
ctccagaagctggacgtgagcagcaacagcatcggctttgtgacccctggcttctttgtccttgccaaccggctg
aaagagcttaacctcagcgccaacgccctgaagacagtggatcccttctggttcggtcgcttaacagagaccctg
aatatcctagacgtgagcgccaacccgctccactgtgcctgcggggcggcctttgtggacttcctgctggagatg

caggcggccgtgcctgggctgtccaggcgcgtcacgtgtggcagtccgggccagctccagggccgcagcatcttc
gcacaggacctgcgcctctgcctggatgagaccctctccttggactgctttggc

Complete nucleotide and amino acid sequences for canine and feline TLR9 are publicly availiable. For example, an amino acid sequence for canine TLR9 is available as GenBank accession number BAC65192 and its corresponding nucleotide sequence is available as GenBank accession number AB104899. An amino acid sequence for feline TLR9 is available as GenBank accession number AAN15751 and its corresponding nucleotide sequence is available as GenBank accession number AY137581.

Complete nucleotide and amino acid sequences for canine and feline TLR9 were also determined independently from those available from public databases.

An amino acid sequence of canine TLR9 is provided as SEQ ID NO:21. Based on comparison with known amino acid sequences of human and murine TLR9, it appears that SEQ ID NO:21 includes sequence for at least a majority of the extracellular domain, all of the transmembrane domain, and at least a portion of the intracellular domain of canine TLR9 (See Figure 1). Amino acids numbered 1-822 of SEQ ID NO:21 are presumptively extracellular domain and correspond to SEQ ID NO:22. SEQ ID NO:23 is a nucleotide sequence of canine TLR9 cDNA having an open reading frame corresponding to nucleotides 91-3186. SEQ ID NO:24 is a nucleotide sequence of canine cDNA encoding amino acids 1-822 of SEQ ID NO:21.

An amino acid sequence of feline TLR9 is provided as SEQ ID NO:25. Based on comparison with known amino acid sequences of human and murine TLR9, it appears that SEQ ID NO:25 includes sequence for at least a majority of the extracellular domain, all of the transmembrane domain, and at least a portion of the intracellular domain of feline TLR9 (See Figure 1). Amino acids numbered 1-820 of SEQ ID NO:25 are presumptively extracellular domain and correspond to SEQ ID NO:26. SEQ ID NO:27 is a nucleotide sequence of feline TLR9 cDNA having an open reading frame corresponding to nucleotides 87-3179. SEQ ID NO:28 is a nucleotide sequence of feline cDNA encoding amino acids 1-820 of SEQ ID NO:25.

SEQ ID NO:21 (Canine TLR9)

MGPCRGALHPLSLLVQAAALALALALAQGTLPAFLPCELQPHGLVNCNWLFLKSVPRFSAAAPRGNVTSLSLYSNRI
HHLHDYDFVHFVHLRRLNLKWNCPPASLSPMHFPCHMTIEPNTFLAVPTLEDLNLSYNSITTVPALPSSLVSLSL
SRTNILVLDPATLAGLYALRFLFLDGNCYYKNPCQQALQVAPGALLGLGNLTHLSLKYNNLTVVPRGLPPSLEYL

LLSYNHIITLAPEDLANLTALRVLDVGGNCRRCDHARNPCRECPKGFPQLHPNTFGHLSHLEGLVLRDSSLYSLD
PRWFHGLGNLMVLDLSENFLYDCITKTKAFYGLARLRRLNLSFNYHKKVSFAHLHLASSFGSLLSLQELDIHGIF
FRSLSKTTLQSLAHLPMLQRLHLQLNFISQAQLSIFGAFPGLRYVDLSDNRISGAAEPAAATGEVEADCGERVWP
QSRDLALGPLGTPGSEAFMPSCRTLNFTLDLSRNNLVTVQPEMFVRLARLQCLGLSHNSISQAVNGSQFVPLSNL
RVLDLSHNKLDLYHGRSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA
SLRALDFSGNTLSQMWAEGDLYLRFFQGLRSLVQLDLSQNRLHTLLPRNLDNLPKSLRLLRLRDNYLAFFNWSSL
ALLPKLEALDLAGNQLKALSNGSLPNGTQLQRLDLSGNSIGFVVPSFFALAVRLRELNLSANALKTVEPSWFGSL
AGALKVLDVTANPLHCACGATFVDFLLEVQAAVPGLPSRVKCGSPGQLQGRSIFAQDLRLCLDEALSWVCFSLSL
LAVALSLAVPMLHQLCGWDLWYCFHLCLAWLPRRGRRRGVDALAYDAFVVFDKAQSSVADWVYNELRVQLEERRG
RRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRLLEDRKDVVVLVILCPDA
HRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGTALTRDNRHFYNQNFCRGPTTA

SEQ ID NO:22 (Canine TLR9)

MGPCRGALHPLSLLVQAAALALALAQGTLPAFLPCELQPHGLVNCNWLFLKSVPRFSAAAPRGNVTSLSLYSNRI
HHLHDYDFVHFVHLRRLNLKWNCPPASLSPMHFPCHMTIEPNTFLAVPTLEDLNLSYNSITTVPALPSSLVSLSL
SRTNILVLDPATLAGLYALRFLFLDGNCYYKNPCQQALQVAPGALLGLGNLTHLSLKYNNLTVVPRGLPPSLEYL
LLSYNHIITLAPEDLANLTALRVLDVGGNCRRCDHARNPCRECPKGFPQLHPNTFGHLSHLEGLVLRDSSLYSLD
PRWFHGLGNLMVLDLSENFLYDCITKTKAFYGLARLRRLNLSFNYHKKVSFAHLHLASSFGSLLSLQELDIHGIF
FRSLSKTTLQSLAHLPMLQRLHLQLNFISQAQLSIFGAFPGLRYVDLSDNRISGAAEPAAATGEVEADCGERVWP
QSRDLALGPLGTPGSEAFMPSCRTLNFTLDLSRNNLVTVQPEMFVRLARLQCLGLSHNSISQAVNGSQFVPLSNL
RVLDLSHNKLDLYHGRSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA
SLRALDFSGNTLSQMWAEGDLYLRFFQGLRSLVQLDLSQNRLHTLLPRNLDNLPKSLRLLRLRDNYLAFFNWSSL
ALLPKLEALDLAGNQLKALSNGSLPNGTQLQRLDLSGNSIGFVVPSFFALAVRLRELNLSANALKTVEPSWFGSL
AGALKVLDVTANPLHCACGATFVDFLLEVQAAVPGLPSRVKCGSPGQLQGRSIFAQDLRLCLDEALSWVCFS

SEQ ID NO:23 (Canine TLR9)

aggaaggggctgtgagctccaagcatcctttcctgcagctgctgcccagcctgccagccagaccctctggagaag
cccccgctccctgtcatgggcccctgccgtggcgccctgcacccctgtctctcctggtgcaggctgccgcgcta
gccctggccctggcccagggcaccctgcctgccttcctgccctgtgagctccagccccatggcctggtgaactgc
aactggctgttcctcaagtccgtgccccgcttctcggcagctgcaccccgcggtaacgtcaccagcctttccttg
tactccaaccgcatccaccacctccatgactatgactttgtccacttcgtccacctgcggcgtctcaatctcaag
tggaactgcccgcccgccagcctcagccccatgcactttccctgtcacatgaccattgagcccaacaccttcctg
gctgtgcccaccctagaggacctgaatctgagctataacagcatcacgactgtgcccgccctgcccagttcgctt
gtgtccctgtccctgagccgcaccaacatcctggtgctggaccctgccaccctggcaggcctttatgccctgcgc
ttcctgttcctggatggcaactgctactacaagaaccctgccagcaggccctgcaggtggccccaggtgccctc
ctgggcctgggcaacctcacacacctgtcactcaagtacaacaacctcaccgtggtgccgcggggcctgcccccc
agcctggagtacctgctcttgtcctacaaccacatcatcaccctggcacctgaggacctggccaatctgactgcc
ctgcgtgtcctcgatgtgggtgggaactgtcgccgctgtgaccatgcccgtaacccctgcagggagtgccccaag
ggcttcccccagctgcaccccaacaccttcggccacctgagccacctcgaaggcctggtgttgagggacagctct
ctctacagcctggaccccaggtggttccatggcctgggcaacctcatggtgctggacctgagtgagaacttcctg
tatgactgcatcaccaaaaccaaagccttctacggcctggcccggctgcgcagactcaacctgtccttcaattat
cataagaaggtgtcctttgcccacctgcatctggcatcctccttcgggagcctactgtccctgcaggagctggac
atacatggcatcttcttccgctcgctcagcaagaccacgctccagtcgctggcccacctgcccatgctccagcgt
ctgcatctgcagttgaactttatcagccaggcccagctcagcatcttcggcgccttccctggactgcggtacgtg
gacttgtcagacaaccgcatcagtggagctgcagagcccgcggctgccacaggggaggtagaggcagactgtggg
gagagagtctggccacagtcccgggaccttgctctgggcccactgggcacccccggctcagaggccttcatgccg
agctgcaggaccctcaacttcaccttggacctgtctcggaacaacctagtgactgttcagccggagatgtttgtc
cggctggcgcgcctccagtgcctgggcctgagccacaacagcatctcgcaggcggtcaatggctcgcagttcgtg
cctctgagcaacctgcgggtgctggacctgtcccataacaagctggacctgtaccacgggcgctcgttcacggag
ctgccgcggctggaggccttggacctcagctacaacagccagcccttcagcatgcggggcgtgggccacaatctc
agctttgtggcacagctgccagccctgcgctacctcagcctggcgcacaatggcatccacagccgcgtgtcccag
cagctccgcagcgcctcgctccgggccctggacttcagtggcaatacctgagccagatgtgggccgagggagac
ctctatctccgcttcttccaaggcctgagaagcctggttcagctggacctgtcccagaatcgcctgcatacctc
ctgccacgcaacctggacaacctccccaagagcctgcggctcctgcggctccgtgacaattacctggctttcttc
aactggagcagcctggccctcctacccaagctggaagccctggacctggcgggaaaccagctgaaggccctgagc

aatggcagcttgcccaacggcacccagctccagaggctggacctcagcggcaacagcatcggcttcgtggtcccc
agctttttgccctggccgtgaggcttcgagagctcaacctcagcgccaacgccctcaagacggtggagccctcc
tggtttggttccctggcgggtgccctgaaagtcctagacgtgaccgccaacccctgcattgcgcttgcggcgca
accttcgtggacttcttgctggaggtgcaggctgcggtgcccggcctgcctagccgtgtcaagtgcggcagcccg
ggccagctccagggccgcagcatcttcgcacaggacctgcgcctctgcctggacgaagcgctctcctgggtctgt
ttcagcctctcgctgctggctgtggccctgagcctggctgtgcccatgctgcaccagctctgtggctgggacctc
tggtactgcttccacctgtgcctggcctggctgccccggcgggggcggcggcggggtgtggatgccctggcctat
gacgccttcgtggtcttcgacaaggcgcagagctcggtggcggactgggtgtacaatgagctgcgggtacagcta
gaggagcgccgtgggcgccgggcgctacgcctgtgtctggaggaacgtgactgggtacccggcaaaaccctcttc
gagaacctctgggcctcagtttacagcagccgcaagacgctgtttgtgctggcccgcacggacagagtcagcggc
ctcctgcgtgccagcttcctgctggcccaacagcgcctgctggaggaccgcaaggacgtcgtggtgctggtgatc
ctgtgccccgacgcccaccgctcccgctatgtgcggctgcgccagcgcctctgccgccagagtgtcctcctctgg
ccccaccagcccagtggccagcgcagcttctgggcccagctgggcacggccctgaccagggacaaccgccacttc
tacaaccagaacttctgccggggccccacgacagcctgataggcagacagcccagcaccttcgcgcccctacacc
ctgcctgtctgtctgggatgcccgacctgctggctctacaccgccgctctgtctcccctacacccagccctggca
taaagcgaccgctcaataaatgctgctggtagac

SEQ ID NO:24 (Canine TLR9)

atgggcccctgccgtggcgccctgcacccctgtctctcctggtgcaggctgccgcgctagccctggccctggcc
cagggcaccctgcctgccttcctgccctgtgagctccagccccatggcctggtgaactgcaactggctgttcctc
aagtccgtgccccgcttctcggcagctgcaccccgcggtaacgtcaccagcctttccttgtactccaaccgcatc
caccacctccatgactatgactttgtccacttcgtccacctgcggcgtctcaatctcaagtggaactgcccgccc
gccagcctcagccccatgcactttccctgtcacatgaccattgagcccaacaccttcctggctgtgcccacccta
gaggacctgaatctgagctataacagcatcacgactgtgcccgccctgcccagttcgcttgtgtccctgtccctg
agccgcaccaacatcctggtgctggaccctgccaccctggcaggcctttatgccctgcgcttcctgttcctggat
ggcaactgctactacaagaacccctgccagcaggccctgcaggtggccccaggtgccctcctgggcctgggcaac
ctcacacacctgtcactcaagtacaacaacctcaccgtggtgccgcggggcctgccccccagcctggagtacctg
ctcttgtcctacaaccacatcatcaccctggcacctgaggacctggccaatctgactgccctgcgtgtcctcgat
gtgggtgggaactgtcgccgctgtgaccatgcccgtaacccctgcagggagtgccccaagggcttcccccagctg
caccccaacaccttcggccacctgagccacctcgaaggcctggtgttgagggacagctctctctacagcctggac
cccaggtggttccatggcctgggcaacctcatggtgctggacctgagtgagaacttcctgtatgactgcatcacc
aaaaccaaagccttctacggcctggcccggctgcgcagactcaacctgtccttcaattatcataagaaggtgtcc
tttgcccacctgcatctggcatcctccttcgggagcctactgtccctgcaggagctggacatacatggcatcttc
ttccgctcgctcagcaagaccacgctccagtcgctggcccacctgcccatgctccagcgtctgcatctgcagttg
aactttatcagccaggcccagctcagcatcttcggcgccttccctggactgcggtacgtggacttgtcagacaac
cgcatcagtggagctgcagagcccgcggctgccacaggggaggtagaggcagactgtggggagagagtctggcca
cagtcccgggaccttgctctgggcccactgggcacccccggctcagaggccttcatgccgagctgcaggaccctc
aacttcaccttggacctgtctcggaacaacctagtgactgttcagccggagatgtttgtccggctggcgcgcctc
cagtgcctgggcctgagccacaacagcatctcgcaggcggtcaatggctcgcagttcgtgcctctgagcaacctg
cgggtgctggacctgtcccataacaagctggacctgtaccacgggcgctcgttcacggagctgccgcggctggag
gccttggacctcagctacaacagccagcccttcagcatgcggggcgtgggccacaatctcagctttgtggcacag
ctgccagccctgcgctacctcagcctggcgcacaatggcatccacagccgcgtgtcccagcagctccgcagcgcc
tcgctccgggccctggacttcagtggcaataccctgagccagatgtgggccgagggagacctctatctccgcttc
ttccaaggcctgagaagcctggttcagctggacctgtcccagaatcgcctgcataccctcctgccacgcaacctg
gacaacctccccaagagcctgcggctcctgcggctccgtgacaattacctggctttcttcaactggagcagcctg
gccctcctacccaagctggaagccctggacctggcgggaaaccagctgaaggccctgagcaatggcagcttgccc
aacggcacccagctccagaggctggacctcagcggcaacagcatcggcttcgtggtccccagctttttgccctg
gccgtgaggcttcgagagctcaacctcagcgccaacgccctcaagacggtggagccctcctggtttggttccctg
gcgggtgccctgaaagtcctagacgtgaccgccaacccttgcattgcgcttgcggcgcaaccttcgtggacttc
ttgctggaggtgcaggctgcggtgcccggcctgcctagccgtgtcaagtgcggcagcccgggccagctccagggc
cgcagcatcttcgcacaggacctgcgcctctgcctggacgaagcgctctcctgggtctgtttcagc

SEQ ID NO:25 (Feline TLR9)

MGPCHGALHPLSLLVQAAALAVALAQGTLPAFLPCELQRHGLVNCDWLFLKSVPHFSAAAPRGNVTSLSLYSNRI
HHLHDSDFVHLSSLRRLNLKWNCPPASLSPMHFPCHMTIEPHTFLAVPTLEELNLSYNSITTVPALPSSLVSLSL

SRTNILVLDPANLAGLHSLRFLFLDGNCYYKNPCPQALQVAPGALLGLGNLTHLSLKYNNLTAVPRGLPPSLEYL
LLSYNHIITLAPEDLANLTALRVLDVGGNCRRCDHARNPCMECPKGFPHLHPDTFSHLNHLEGLVLKDSSLYNLN
PRWFHALGNLMVLDLSENFLYDCITKTTAFQGLAQLRRLNLSFNYHKKVSFAHLHLAPSFGSLLSLQQLDMHGIF
FRSLSETTLRSLVHLPMLQSLHLQMNFINQAQLSIFGAFPGLRYVDLSDNRISGAMELAAATGEVDGGERVRLPS
GDLALGPPGTPSSEGFMPGCKTLNFTLDLSRNNLVTIQPEMFARLSRLQCLLLSRNSISQAVNGSQFMPLTSLQV
LDLSHNKLDLYHGRSFTELPRLEALDLSYNSQPFSMQGVGHNLSFVAQLPALRYLSLAHNDIHSRVSQQLCSASL
RALDFSGNALSRMWAEGDLYLHFFRGLRSLVRLDLSQNRLHTLLPRTLDNLPKSLRLLRLRDNYLAFFNWSSLVL
LPRLEALDLAGNQLKALSNGSLPNGTQLQRLDLSSNSISFVASSFFALATRLRELNLSANALKTVEPSWFGSLAG
TLKVLDVTGNPLHCACGAAFVDFLLEVQAAVPGLPGHVKCGSPGQLQGRSIFAQDLRLCLDEALSWDCFGLSLLT
VALGLAVPMLHHLCGWDLWYCFHLCLAWLPRRGRRRGADALPYDAFVVFDKAQSAVADWVYNELRVRLEERRGRR
ALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRLLEDRKDVVVLVILRPDAHR
SRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGTALTRDNQHFYNQNFCRGPTTAE

SEQ ID NO:26 (Feline TLR9)

MGPCHGALHPLSLLVQAAALAVALAQGTLPAFLPCELQRHGLVNCDWLFLKSVPHFSAAAPRGNVTSLSLYSNRI
HHLHDSDFVHLSSLRRLNLKWNCPPASLSPMHFPCHMTIEPHTFLAVPTLEELNLSYNSITTVPALPSSLVSLSL
SRTNILVLDPANLAGLHSLRFLFLDGNCYYKNPCPQALQVAPGALLGLGNLTHLSLKYNNLTAVPRGLPPSLEYL
LLSYNHIITLAPEDLANLTALRVLDVGGNCRRCDHARNPCMECPKGFPHLHPDTFSHLNHLEGLVLKDSSLYNLN
PRWFHALGNLMVLDLSENFLYDCITKTTAFQGLAQLRRLNLSFNYHKKVSFAHLHLAPSFGSLLSLQQLDMHGIF
FRSLSETTLRSLVHLPMLQSLHLQMNFINQAQLSIFGAFPGLRYVDLSDNRISGAMELAAATGEVDGGERVRLPS
GDLALGPPGTPSSEGFMPGCKTLNFTLDLSRNNLVTIQPEMFARLSRLQCLLLSRNSISQAVNGSQFMPLTSLQV
LDLSHNKLDLYHGRSFTELPRLEALDLSYNSQPFSMQGVGHNLSFVAQLPALRYLSLAHNDIHSRVSQQLCSASL
RALDFSGNALSRMWAEGDLYLHFFRGLRSLVRLDLSQNRLHTLLPRTLDNLPKSLRLLRLRDNYLAFFNWSSLVL
LPRLEALDLAGNQLKALSNGSLPNGTQLQRLDLSSNSISFVASSFFALATRLRELNLSANALKTVEPSWFGSLAG
TLKVLDVTGNPLHCACGAAFVDFLLEVQAAVPGLPGHVKCGSPGQLQGRSIFAQDLRLCLDEALSWDCFG

SEQ ID NO:27 (Feline TLR9)

agggtctgcgagctccaggcattcttctctgccatcgctgcccagtctgccatccagaccctctggagaagcccc
cactccctgtcatgggcccctgccatggcgccctgcacccccctgtctctcctggtgcaggctgccgcgctggccg
tggccctggcccagggcaccctgcctgcctttctgccctgtgagctccagcgccacggcctggtgaattgcgact
ggctgttcctcaagtccgtgccccacttctcggcggcagcgccccgtggtaacgtcaccagcctttccctgtact
ccaaccgcatccaccacctccacgactccgactttgtccacctgtccagcctgcggcgtctcaacctcaaatgga
actgcccacccgccagcctcagccccatgcacttcccctgtcacatgaccattgagccccacaccttcctggccg
tgcccaccctggaggagctgaacctgagctacaacagcatcacgacagtacccgccctgcccagttccctcgtgt
ccctgtccttgagccgtaccaacatcctggtgctggaccctgccaacctcgcagggctgcactccctgcgctttc
tgttcctggatggcaactgctactacaagaacccctgcccgcaggccctgcaggtggccccgggcgccctccttg
gcctgggcaaccttacgcacctgtcactcaagtacaacaacctcactgcggtgccccgcggcctgccccccagcc
tggagtacctgctattgtcctacaaccacatcatcaccctggcacctgaggacctggccaacctgaccgccctgc
gtgtgctcgatgtgggtgggaactgccgtcgctgtgaccacgcccgcaacccctgtatggagtgccccaagggct
tcccgcacctgcaccctgacaccttcagccacctgaaccacctcgaaggcctggtgttgaaggacagctctctct
acaacctgaaccccagatggttccatgccctgggcaacctcatggtgctggacctgagtgagaacttcctatatg
actgcatcaccaaaaccacagccttccagggcctggcccagctgcgcagactcaacttgtctttcaattaccaca
agaaggtgtcctttgcccacctgcatctggcgccctccttcgggagcctgctctccctgcagcagctggacatgc
atggcatcttcttccgctcgctcagcgagaccacgctccggtcgctggtccacctgcccatgctccagagtctgc
acctgcagatgaacttcatcaatcaggcccagctcagcatcttcggggccttccctggcctgcgatacgtggacc
tgtcagacaaccgcataagtggagccatggagctggcggctgccacgggggaggtggatggtggggagagagtcc
ggctgccatctggggacctagctctgggcccaccgggcacccctagctccgagggcttcatgccaggctgcaaga
ccctcaacttcaccttggacctgtcacggaacaacctagtgacaatccagccagagatgtttgcccggctctcgc
gcctccagtgcctgctcctgagccgcaacagcatctcgcaggcagtcaacggctcacaatttatgccgctgacca
gcctgcaggtgctggacctgtcccataacaagctggacctgtaccatgggcgctctttcacggagctgccgcggc
tggaggccctggacctcagctacaacagccagcccttcagcatgcagggcgtgggtcacaacctcagctttgtgg
cacagctgccggccctgcgctatctcagcctggcgcacaacgacatccacagccgtgtgtcccagcagctctgca
gcgcctcgctgcgggccttggacttcagcggcaatgccttgagccggatgtgggccgagggagacctgtatctcc
acttcttccgaggcctgaggagcctggtccggttggatctgtcccagaatcgcctgcataccctcttgccacgca
ccctggacaacctccccaagagcctgcggctgctgcgtctccgtgacaattatctggctttcttcaactggagca

gcctggtcctcctccccaggctggaagccctggacctggcgggaaaccagctgaaggccctgagcaacggcagct
tgcctaatggaacccagctccagaggctggacctcagcagcaacagtatcagcttcgtggcctccagcttttttg
ctctggccaccaggctgcgagagctcaacctcagtgccaacgccctcaagacggtggagccctcctggttcggtt
ctctagcgggcaccctgaaagtcctagatgtgactggcaacccccctgcactgcgcctgtggggcggccttcgtgg
acttcttgctggaggtgcaggctgcagtgcccggcctgccaggccacgtcaagtgtggcagtccaggtcagctcc
agggccgcagcatctttgcgcaggatctgcgcctctgcctggatgaggccctctcctgggactgttttggcctct
cgctgctgaccgtggccctgggcctggccgtgcccatgctgcaccacctctgtggctgggacctctggtactgct
tccacctgtgcctggcctggctgccccggcgggggcggcggcggggcgcggatgccctgccctacgatgccttg
tggtcttcgacaaggcacagagcgcggtggccgactgggtgtacaacgagctgcgggtacggctagaggagcgcc
gtggacgccgagcgctccgcctgtgcctggaggaacgtgactggctacccggtaaaacgctctttgagaacctgt
gggcctcagtttacagcagccgcaagatgctgtttgtgctggcccacacagacagggtcagcggcctcttgcgcg
ccagctttctgctggcccagcagcgcctgctggaggaccgcaaggacgttgtggtgctggtgatcctgcgccccg
acgcccaccgctcccgctatgtgcggctgcgccagcgcctctgccgccagagcgtcctcctctggccccaccagc
ccagtggccagcgcagcttctgggcccagctgggcacggccctgaccagggacaaccagcacttctataaccaga
acttctgccggggccccacgacggcagagtgaccgcccagcaccccaagcctcctacaccttgcctgtctgcctg
ggatgccggg

SEQ ID NO:28 (Feline TLR9)

atgggcccctgccatggcgccctgcacccctgtctctcctggtgcaggctgccgcgctggccgtggccctggcc
cagggcaccctgcctgcctttctgccctgtgagctccagcgccacggcctggtgaattgcgactggctgttcctc
aagtccgtgccccacttctcggcggcagcgccccgtggtaacgtcaccagcctttccctgtactccaaccgcatc
caccacctccacgactccgactttgtccacctgtccagcctgcggcgtctcaacctcaaatggaactgcccaccc
gccagcctcagccccatgcacttcccctgtcacatgaccattgagccccacaccttcctggccgtgcccaccctg
gaggagctgaacctgagctacaacagcatcacgacagtacccgccctgcccagttccctcgtgtccctgtccttg
agccgtaccaacatcctggtgctggaccctgccaacctcgcagggctgcactccctgcgctttctgttcctggat
ggcaactgctactacaagaacccctgcccgcaggccctgcaggtggccccgggcgccctccttggcctgggcaac
cttacgcacctgtcactcaagtacaacaacctcactgcggtgccccgcggcctgccccccagcctggagtacctg
ctattgtcctacaaccacatcatcaccctggcacctgaggacctggccaacctgaccgccctgcgtgtgctcgat
gtgggtgggaactgccgtcgctgtgaccacgcccgcaacccctgtatggagtgccccaagggcttcccgcacctg
caccctgacaccttcagccacctgaaccacctcgaaggcctggtgttgaaggacagctctctctacaacctgaac
cccagatggttccatgccctgggcaacctcatggtgctggacctgagtgagaacttcctatatgactgcatcacc
aaaaccacagccttccagggcctggcccagctgcgcagactcaacttgtctttcaattaccacaagaaggtgtcc
tttgcccacctgcatctggcgccctccttcgggagcctgctctccctgcagcagctggacatgcatggcatcttc
ttccgctcgctcagcgagaccacgctccggtcgctggtccacctgcccatgctccagagtctgcacctgcagatg
aacttcatcaatcaggcccagctcagcatcttcggggccttccctggcctgcgatacgtggacctgtcagacaac
cgcataagtggagccatggagctggcggctgccacgggggaggtggatggtggggagagagtccggctgccatct
ggggacctagctctgggcccaccgggcacccctagctccgagggcttcatgccaggctgcaagaccctcaacttc
accttggacctgtcacggaacaacctagtgacaatccagccagagatgtttgcccggctctcgcgcctccagtgc
ctgctcctgagccgcaacagcatctcgcaggcagtcaacggctcacaatttatgccgctgaccagcctgcaggtg
ctggacctgtcccataacaagctggacctgtaccatgggcgctctttcacggagctgccgcggctggaggccctg
gacctcagctacaacagccagcccttcagcatgcagggcgtgggtcacaacctcagctttgtggcacagctgccg
gccctgcgctatctcagcctggcgcacaacgacatccacagccgtgtgtcccagcagctctgcagcgcctcgctg
cgggccttggacttcagcggcaatgccttgagccggatgtgggccgagggagacctgtatctccacttcttccga
ggcctgaggagcctggtccggttggatctgtcccagaatcgcctgcataccctcttgccacgcaccctggacaac
ctccccaagagcctgcggctgctgcgtctccgtgacaattatctggctttcttcaactggagcagcctggtcctc
ctccccaggctggaagccctggacctggcgggaaaccagctgaaggccctgagcaacggcagcttgcctaatgga
acccagctccagaggctggacctcagcagcaacagtatcagcttcgtggcctccagctttttgctctggccacc
aggctgcgagagctcaacctcagtgccaacgccctcaagacggtggagccctcctggttcggttctctagcgggc
accctgaaagtcctagatgtgactggcaacccccctgcactgcgcctgtggggcggccttcgtggacttcttgctg
gaggtgcaggctgcagtgcccggcctgccaggccacgtcaagtgtggcagtccaggtcagctccagggccgcagc
atctttgcgcaggatctgcgcctctgcctggatgaggccctctcctgggactgttttggc

Complete nucleotide and amino acid sequences for murine and human TLR9 are publicly available. For example, an amino acid sequence of murine TLR9 is available as

GenBank accession no. AAK29625, provided as SEQ ID NO:29. Amino acids numbered 1-821 of SEQ ID NO:29 presumptively include the entire extracellular domain and correspond to SEQ ID NO:30. SEQ ID NO:31 corresponds to GenBank accession number AF348140, which is a nucleotide sequence of murine TLR9 cDNA. SEQ ID NO:32 is a nucleotide sequence of murine cDNA encoding amino acids 1-821 of SEQ ID NO:29.

An amino acid sequence of human TLR9 is available as GenBank accession no. AAF78037, provided as SEQ ID NO:33. Amino acids numbered 1-820 of SEQ ID NO:33 presumptively include the entire extracellular domain and correspond to SEQ ID NO:34. SEQ ID NO:35 corresponds to GenBank accession number AF245704, which is a nucleotide sequence of human TLR9 cDNA. SEQ ID NO:36 is a nucleotide sequence of human cDNA encoding amino acids 1-820 of SEQ ID NO:33.

SEQ ID NO:29 (Murine TLR9)

MVLRRRTLHPLSLLVQAAVLAETLALGTLPAFLPCELKPHGLVDCNWLFLKSVPRFSAAASCSNITRLSLISNRI
HHLHNSDFVHLSNLRQLNLKWNCPPTGLSPLHFSCHMTIEPRTFLAMRTLEELNLSYNGITTVPRLPSSLVNLSL
SHTNILVLDANSLAGLYSLRVLFMDGNCYYKNPCTGAVKVTPGALLGLSNLTHLSLKYNNLTKVPRQLPPSLEYL
LVSYNLIVKLGPEDLANLTSLRVLDVGGNCRRCDHAPNPCIECGQKSLHLHPETFHHLSHLEGLVLKDSSLHTLN
SSWFQGLVNLSVLDLSENFLYESINHTNAFQNLTRLRKLNLSFNYRKKVSFARLHLASSFKNLVSLQELNMNGIF
FRSLNKYTLRWLADLPKLHTLHLQMNFINQAQLSIFGTFRALRFVDLSDNRISGPSTLSEATPEEADDAEQEELL
SADPHPAPLSTPASKNFMDRCKNFKFTMDLSRNNLVTIKPEMFVNLSRLQCLSLSHNSIAQAVNGSQFLPLTNLQ
VLDLSHNKLDLYHWKSFSELPQLQALDLSYNSQPFSMKGIGHNFSFVAHLSMLHSLSLAHNDIHTRVSSHLNSNS
VRFLDFSGNGMGRMWDEGGLYLHFFQGLSGLLKLDLSQNNLHILRPQNLDNLPKSLKLLSLRDNYLSFFNWTSLS
FLPNLEVLDLAGNQLKALTNGTLPNGTLLQKLDVSSNSIVSVVPAFFALAVELKEVNLSHNILKTVDRSWFGPIV
MNLTVLDVRSNPLHCACGAAFVDLLLEVQTKVPGLANGVKCGSPGQLQGRSIFAQDLRLCLDEVLSWDCFGLSLL
AVAVGMVVPILHHLCGWDVWYCFHLCLAWLPLLARSRRSAQALPYDAFVVFDKAQSAVADWVYNELRVRLEERRG
RRALRLCLEDRDWLPGQTLFENLWASIYGSRKTLFVLAHTDRVSGLLRTSFLLAQQRLLEDRKDVVVLVILRPDA
HRSRYVRLRQRLCRQSVLFWPQQPNGQGGFWAQLSTALTRDNRHFYNQNFCRGPTAE

SEQ ID NO:30 (Murine TLR9)

MVLRRRTLHPLSLLVQAAVLAETLALGTLPAFLPCELKPHGLVDCNWLFLKSVPRFSAAASCSNITRLSLISNRI
HHLHNSDFVHLSNLRQLNLKWNCPPTGLSPLHFSCHMTIEPRTFLAMRTLEELNLSYNGITTVPRLPSSLVNLSL
SHTNILVLDANSLAGLYSLRVLFMDGNCYYKNPCTGAVKVTPGALLGLSNLTHLSLKYNNLTKVPRQLPPSLEYL
LVSYNLIVKLGPEDLANLTSLRVLDVGGNCRRCDHAPNPCIECGQKSLHLHPETFHHLSHLEGLVLKDSSLHTLN
SSWFQGLVNLSVLDLSENFLYESINHTNAFQNLTRLRKLNLSFNYRKKVSFARLHLASSFKNLVSLQELNMNGIF
FRSLNKYTLRWLADLPKLHTLHLQMNFINQAQLSIFGTFRALRFVDLSDNRISGPSTLSEATPEEADDAEQEELL
SADPHPAPLSTPASKNFMDRCKNFKFTMDLSRNNLVTIKPEMFVNLSRLQCLSLSHNSIAQAVNGSQFLPLTNLQ
VLDLSHNKLDLYHWKSFSELPQLQALDLSYNSQPFSMKGIGHNFSFVAHLSMLHSLSLAHNDIHTRVSSHLNSNS
VRFLDFSGNGMGRMWDEGGLYLHFFQGLSGLLKLDLSQNNLHILRPQNLDNLPKSLKLLSLRDNYLSFFNWTSLS
FLPNLEVLDLAGNQLKALTNGTLPNGTLLQKLDVSSNSIVSVVPAFFALAVELKEVNLSHNILKTVDRSWFGPIV
MNLTVLDVRSNPLHCACGAAFVDLLLEVQTKVPGLANGVKCGSPGQLQGRSIFAQDLRLCLDEVLSWDCFG

SEQ ID NO:31 (Murine TLR9)

tgtcagagggagcctcgggagaatcctccatctcccaacatggttctccgtcgaaggactctgcacccccttgtcc
ctcctggtacaggctgcagtgctggctgagactctggccctgggtaccctgcctgccttcctaccctgtgagctg

aagcctcatggcctggtggactgcaattggctgttcctgaagtctgtaccccgtttctctgcggcagcatcctgc
tccaacatcacccgcctctccttgatctccaaccgtatccaccacctgcacaactccgacttcgtccacctgtcc
aacctgcggcagctgaacctcaagtggaactgtccacccactggccttagccccctgcacttctcttgccacatg
accattgagcccagaaccttcctggctatgcgtacactggaggagctgaacctgagctataatggtatcaccact
gtgccccgactgcccagctccctggtgaatctgagcctgagccacaccaacatcctggttctagatgctaacagc
ctcgccggcctatacagcctgcgcgttctcttcatggacgggaactgctactacaagaacccctgcacaggagcg
gtgaaggtgaccccaggcgccctcctgggcctgagcaatctcacccatctgtctctgaagtataacaacctcaca
aaggtgccccgccaactgccccccagcctggagtacctcctggtgtcctataacctcattgtcaagctggggcct
gaagacctggccaatctgacctcccttcgagtacttgatgtgggtgggaattgccgtcgctgcgaccatgccccc
aatccctgtatagaatgtggccaaaagtccctccacctgcaccctgagaccttccatcacctgagccatctggaa
ggcctggtgctgaaggacagctctctccatacactgaactcttcctggttccaaggtctggtcaacctctcggtg
ctggacctaagcgagaactttctctatgaaagcatcaaccacaccaatgcctttcagaacctaacccgcctgcgc
aagctcaacctgtccttcaattaccgcaagaaggtatcctttgcccgcctccacctggcaagttccttcaagaac
ctggtgtcactgcaggagctgaacatgaacggcatcttcttccgctcgctcaacaagtacacgctcagatggctg
gccgatctgcccaaactccacactctgcatcttcaaatgaacttcatcaaccaggcacagctcagcatctttggt
accttccgagcccttcgctttgtggacttgtcagacaatcgcatcagtgggccttcaacgctgtcagaagccacc
cctgaagaggcagatgatgcagagcaggaggagctgttgtctgcggatcctcacccagctccactgagcacccct
gcttctaagaacttcatggacaggtgtaagaacttcaagttcaccatggacctgtctcggaacaacctggtgact
atcaagccagagatgtttgtcaatctctcacgcctccagtgtcttagcctgagccacaactccattgcacaggct
gtcaatggctctcagttcctgccgctgactaatctgcaggtgctggacctgtcccataacaaactggacttgtac
cactggaaatcgttcagtgagctaccacagttgcaggccctggacctgagctacaacagccagccctttagcatg
aagggtataggccacaatttcagttttgtggcccatctgtccatgctacacagccttagcctggcacacaatgac
attcatacccgtgtgtcctcacatctcaacagcaactcagtgaggtttcttgacttcagcggcaacggtatgggc
cgcatgtgggatgaggggggcctttatctccatttcttccaaggcctgagtggcctgctgaagctggacctgtct
caaaataacctgcatatcctccggccccagaaccttgacaacctccccaagagcctgaagctgctgagcctccga
gacaactacctatctttctttaactggaccagtctgtccttcctgcccaacctggaagtcctagacctggcaggc
aaccagctaaaggccctgaccaatggcaccctgcctaatggcaccctcctccagaaactggatgtcagcagcaac
agtatcgtctctgtggtcccagccttcttcgctctggcggtcgagctgaaagaggtcaacctcagccacaacatt
ctcaagacggtggatcgctcctggtttgggcccattgtgatgaacctgacagttctagacgtgagaagcaaccct
ctgcactgtgcctgtggggcagccttcgtagacttactgttggaggtgcagaccaaggtgcctggcctggctaat
ggtgtgaagtgtggcagccccggccagctgcagggccgtagcatcttcgcacaggacctgcggctgtgcctggat
gaggtcctctcttgggactgctttggcctttcactcttggctgtggccgtgggcatggtggtgcctatactgcac
catctctgcggctgggacgtctggtactgttttcatctgtgcctggcatggctacctttgctggcccgcagccga
cgcagcgcccaagctctcccctatgatgccttcgtggtgttcgataaggcacagagcgcagttgcggactgggtg
tataacgagctgcgggtgcggctggaggagcggcgcggtcgccgagccctacgcttgtgtctggaggaccgagat
tggctgcctggccagacgctcttcgagaaccctctgggcttccatctatgggagccgcaagactctatttgtgctg
gcccacacggaccgcgtcagtggcctcctgcgcaccagcttcctgctggctcagcagcgcctgttggaagaccgc
aaggacgtggtggtgttggtgatcctgcgtccggatgcccaccgctcccgctatgtgcgactgcgccagcgtctc
tgccgccagagtgtgctcttctggccccagcagcccaacgggcaggggggcttctgggcccagctgagtacagcc
ctgactagggacaaccgccacttctataaccagaacttctgccggggacctacagcagaatagctcagagcaaca
gctggaaacagctgcatcttcatgcctggttcccgagttgctctgcctgc

SEQ ID NO:31 (Murine TLR9)

atggttctccgtcgaaggactctgcacccctgtccctcctggtacaggctgcagtgctggctgagactctggcc
ctgggtaccctgcctgccttcctaccctgtgagctgaagcctcatggcctggtggactgcaattggctgttcctg
aagtctgtaccccgtttctctgcggcagcatcctgctccaacatcacccgcctctccttgatctccaaccgtatc
caccacctgcacaactccgacttcgtccacctgtccaacctgcggcagctgaacctcaagtggaactgtccaccc
actggccttagcccctgcacttctcttgccacatgaccattgagcccagaaccttcctggctatgcgtacactg
gaggagctgaacctgagctataatggtatcaccactgtgccccgactgcccagctccctggtgaatctgagcctg
agccacaccaacatcctggttctagatgctaacagcctcgccggcctatacagcctgcgcgttctcttcatggac
gggaactgctactacaagaacccctgcacaggagcggtgaaggtgaccccaggcgccctcctgggcctgagcaat
ctcacccatctgtctctgaagtataacaacctcacaaaggtgccccgccaactgccccccagcctggagtacctc
ctggtgtcctataacctcattgtcaagctggggcctgaagacctggccaatctgacctcccttcgagtacttgat
gtgggtgggaattgccgtcgctgcgaccatgcccccaatccctgtatagaatgtggccaaaagtccctccacctg
caccctgagaccttccatcacctgagccatctggaaggcctggtgctgaaggacagctctctccatacactgaac
tcttcctggttccaaggtctggtcaacctctcggtgctggacctaagcgagaactttctctatgaaagcatcaac
cacaccaatgcctttcagaacctaacccgcctgcgcaagctcaacctgtccttcaattaccgcaagaaggtatcc

tttgcccgcctccacctggcaagttccttcaagaacctggtgtcactgcaggagctgaacatgaacggcatcttc
ttccgctcgctcaacaagtacacgctcagatggctggccgatctgcccaaactccacactctgcatcttcaaatg
aacttcatcaaccaggcacagctcagcatctttggtaccttccgagcccttcgctttgtggacttgtcagacaat
cgcatcagtgggccttcaacgctgtcagaagccacccctgaagaggcagatgatgcagagcaggaggagctgttg
tctgcggatcctcacccagctccactgagcacccctgcttctaagaacttcatggacaggtgtaagaacttcaag
ttcaccatggacctgtctcggaacaacctggtgactatcaagccagagatgtttgtcaatctctcacgcctccag
tgtcttagcctgagccacaactccattgcacaggctgtcaatggctctcagttcctgccgctgactaatctgcag
gtgctggacctgtcccataacaaactggacttgtaccactggaaatcgttcagtgagctaccacagttgcaggcc
ctggacctgagctacaacagccagccctttagcatgaagggtataggccacaatttcagttttgtggcccatctg
tccatgctacacagccttagcctggcacacaatgacattcatacccgtgtgtcctcacatctcaacagcaactca
gtgaggtttcttgacttcagcggcaacggtatgggccgcatgtgggatgagggggccttatctccatttcttc
caaggcctgagtggcctgctgaagctggacctgtctcaaaataacctgcatatcctccggccccagaaccttgac
aacctccccaagagcctgaagctgctgagcctccgagacaactacctatctttctttaactggaccagtctgtcc
ttcctgcccaacctggaagtcctagacctggcaggcaaccagctaaaggccctgaccaatggcaccctgcctaat
ggcaccctcctccagaaactggatgtcagcagcaacagtatcgtctctgtggtcccagccttcttcgctctggcg
gtcgagctgaaagaggtcaacctcagccacaacattctcaagacggtggatcgctcctggtttgggcccattgtg
atgaacctgacagttctagacgtgagaagcaaccctctgcactgtgcctgtggggcagccttcgtagacttactg
ttggaggtgcagaccaaggtgcctggcctggctaatggtgtgaagtgtggcagccccggccagctgcagggccgt
agcatcttcgcacaggacctgcggctgtgcctggatgaggtcctctcttgggactgctttggc

SEQ ID NO:33 (Human TLR9)

MGFCRSALHPLSLLVQAIMLAMTLALGTLPAFLPCELQPHGLVNCNWLFLKSVPHFSMAAPRGNVTSLSLSSNRI
HHLHDSDFAHLPSLRHLNLKWNCPPVGLSPMHFPCHMTIEPSTFLAVPTLEELNLSYNNIMTVPALPKSLISLSL
SHTNILMLDSASLAGLHALRFLFMDGNCYYKNPCRQALEVAPGALLGLGNLTHLSLKYNNLTVVPRNLPSSLEYL
LLSYNRIVKLAPEDLANLTALRVLDVGGNCRRCDHAPNPCMECPRHFPQLHPDTFSHLSRLEGLVLKDSSLSWLN
ASWFRGLGNLRVLDLSENFLYKCITKTKAFQGLTQLRKLNLSFNYQKRVSFAHLSLAPSFGSLVALKELDMHGIF
FRSLDETTLRPLARLPMLQTLRLQMNFINQAQLGIFRAFPGLRYVDLSDNRISGASELTATMGEADGGEKVWLQP
GDLAPAPVDTPSSEDFRPNCSTLNFTLDLSRNNLVTVQPEMFAQLSHLQCLRLSHNCISQAVNGSQFLPLTGLQV
LDLSRNKLDLYHEHSFTELPRLEALDLSYNSQPFGMQGVGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCSTSL
RALDFSGNALGHMWAEGDLYLHFFQGLSGLIWLDLSQNRLHTLLPQTLRNLPKSLQVLRLRDNYLAFFKWWSLHF
LPKLEVLDLAGNRLKALTNGSLPAGTRLRRLDVSCNSISFVAPGFFSKAKELRELNLSANALKTVDHSWFGPLAS
ALQILDVSANPLHCACGAAFMDFLLEVQAAVPGLPSRVKCGSPGQLQGLSIFAQDLRLCLDEALSWDCFALSLLA
VALGLGVPMLHHLCGWDLWYCFHLCLAWLPWRGRQSGRDEDALPYDAFVVFDKTQSAVADWVYNELRGQLEECRG
RWALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRLLEDRKDVVVLVILSPDG
RRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGMALTRDNHHFYNRNFCQGPTAE

SEQ ID NO:34 (Human TLR9)

MGFCRSALHPLSLLVQAIMLAMTLALGTLPAFLPCELQPHGLVNCNWLFLKSVPHFSMAAPRGNVTSLSLSSNRI
HHLHDSDFAHLPSLRHLNLKWNCPPVGLSPMHFPCHMTIEPSTFLAVPTLEELNLSYNNIMTVPALPKSLISLSL
SHTNILMLDSASLAGLHALRFLFMDGNCYYKNPCRQALEVAPGALLGLGNLTHLSLKYNNLTVVPRNLPSSLEYL
LLSYNRIVKLAPEDLANLTALRVLDVGGNCRRCDHAPNPCMECPRHFPQLHPDTFSHLSRLEGLVLKDSSLSWLN
ASWFRGLGNLRVLDLSENFLYKCITKTKAFQGLTQLRKLNLSFNYQKRVSFAHLSLAPSFGSLVALKELDMHGIF
FRSLDETTLRPLARLPMLQTLRLQMNFINQAQLGIFRAFPGLRYVDLSDNRISGASELTATMGEADGGEKVWLQP
GDLAPAPVDTPSSEDFRPNCSTLNFTLDLSRNNLVTVQPEMFAQLSHLQCLRLSHNCISQAVNGSQFLPLTGLQV
LDLSRNKLDLYHEHSFTELPRLEALDLSYNSQPFGMQGVGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCSTSL
RALDFSGNALGHMWAEGDLYLHFFQGLSGLIWLDLSQNRLHTLLPQTLRNLPKSLQVLRLRDNYLAFFKWWSLHF
LPKLEVLDLAGNRLKALTNGSLPAGTRLRRLDVSCNSISFVAPGFFSKAKELRELNLSANALKTVDHSWFGPLAS
ALQILDVSANPLHCACGAAFMDFLLEVQAAVPGLPSRVKCGSPGQLQGLSIFAQDLRLCLDEALSWDCFA

SEQ ID NO:35 (Human TLR9)

aggctggtataaaaatcttacttcctctattctctgagccgctgctgcccctgtgggaagggacctcgagtgtga
agcatccttccctgtagctgctgtccagtctgcccgccagaccctctggagaagcccctgccccccagcatgggt
ttctgccgcagcgccctgcacccgctgtctctcctggtgcaggccatcatgctggccatgaccctggccctgggt

accttgcctgccttcctaccctgtgagctccagccccacggcctggtgaactgcaactggctgttcctgaagtct
gtgccccacttctccatggcagcaccccgtggcaatgtcaccagcctttccttgtcctccaaccgcatccaccac
ctccatgattctgactttgcccacctgcccagcctgcggcatctcaacctcaagtggaactgcccgccggttggc
ctcagccccatgcacttcccctgccacatgaccatcgagcccagcaccttcttggctgtgcccaccctggaagag
ctaaacctgagctacaacaacatcatgactgtgcctgcgctgcccaaatccctcatatccctgtccctcagccat
accaacatcctgatgctagactctgccagcctcgccggcctgcatgccctgcgcttcctattcatggacggcaac
tgttattacaagaacccctgcaggcaggcactggaggtggccccgggtgccctccttggcctgggcaacctcacc
cacctgtcactcaagtacaacaacctcactgtggtgccccgcaacctgccttccagcctggagtatctgctgttg
tcctacaaccgcatcgtcaaactggcgcctgaggacctggccaatctgaccgccctgcgtgtgctcgatgtgggc
ggaaattgccgccgctgcgaccacgctcccaacccctgcatggagtgccctcgtcacttcccccagctacatccc
gataccttcagccacctgagccgtcttgaaggcctggtgttgaaggacagttctctctcctggctgaatgccagt
tggttccgtgggctgggaaacctccgagtgctggacctgagtgagaacttcctctacaaatgcatcactaaaacc
aaggccttccagggcctaacacagctgcgcaagcttaacctgtccttcaattaccaaaagagggtgtcctttgcc
cacctgtctctggcccctttccttcgggagcctggtcgccctgaaggagctggacatgcacggcatcttcttccgc
tcactcgatgagaccacgctccggccactggcccgcctgcccatgctccagactctgcgtctgcagatgaacttc
atcaaccaggcccagctcggcatcttcagggccttccctggcctgcgctacgtggacctgtcggacaaccgcatc
agcggagcttcggagctgacagccaccatgggggaggcagatggaggggagaaggtctggctgcagcctggggac
cttgctccggccccagtggacactcccagctctgaagacttcaggcccaactgcagcaccctcaacttcaccttg
gatctgtcacggaacaacctggtgaccgtgcagccggagatgtttgcccagctctcgcacctgcagtgcctgcgc
ctgagccacaactgcatctcgcaggcagtcaatggctcccagttcctgccgctgaccggtctgcaggtgctagac
ctgtcccgcaataagctggacctctaccacgagcactcattcacggagctaccgcgactggaggccctggacctc
agctacaacagccagcccttggcatgcagggcgtgggccacaacttcagcttcgtggctcacctgcgcaccctg
cgccacctcagcctggcccacaacaacatccacagccaagtgtcccagcagctctgcagtacgtcgctgcgggcc
ctggacttcagcggcaatgcactgggccatatgtgggccgagggagacctctatctgcacttcttccaaggcctg
agcggtttgatctggctggacttgtcccagaaccgcctgcacaccctcctgccccaaaccctgcgcaacctcccc
aagagcctacaggtgctgcgtctccgtgacaattacctggccttctttaagtggtggagcctccacttcctgccc
aaactggaagtcctcgacctggcaggaaaccggctgaaggccctgaccaatggcagcctgcctgctggcacccgg
ctccggaggctggatgtcagctgcaacagcatcagcttcgtggcccccggcttcttttccaaggccaaggagctg
cgagagctcaaccttagcgccaacgccctcaagacagtggaccactcctggtttgggcccctggcgagtgccctg
caaatactagatgtaagcgccaaccctctgcactgcgcctgtggggcggcctttatggacttcctgctggaggtg
caggctgccgtgcccggtctgcccagccgggtgaagtgtggcagtccgggccagctccagggcctcagcatcttt
gcacaggacctgcgcctctgcctggatgaggccctctcctgggactgtttcgccctctcgctgctggctgtggct
ctgggcctgggtgtgcccatgctgcatcacctctgtggctgggacctctggtactgcttccacctgtgcctggcc
tggcttccctggcgggggcggcaaagtgggcgagatgaggatgccctgccctacgatgccttcgtggtcttcgac
aaaacgcagagcgcagtggcagactgggtgtacaacgagcttcgggggcagctggaggagtgccgtgggcgctgg
gcactccgcctgtgcctggaggaacgcgactggctgcctggcaaaaccctctttgagaacctgtgggcctcggtc
tatggcagccgcaagacgctgtttgtgctggcccacacggaccgggtcagtggtctcttgcgcgccagcttcctg
ctggcccagcagcgcctgctggaggaccgcaaggacgtcgtggtgctggtgatcctgagccctgacggccgccgc
tcccgctacgtgcggctgcgccagcgcctctgccgccagagtgtcctcctctggccccaccagcccagtggtcag
cgcagcttctgggcccagctgggcatggccctgaccagggacaaccaccacttctataaccggaacttctgccag
ggacccacggccgaatagccgtgagccggaatcctgcacggtgccacctccacactcacctcacctctgcctgcc
tggtctgaccctcccctgctcgcctccctcaccccacacctgacacagagca

SEQ ID NO:36 (Human TLR9)

atgggtttctgccgcagcgccctgcacccgctgtctctcctggtgcaggccatcatgctggccatgaccctggcc
ctgggtaccttgcctgccttcctaccctgtgagctccagccccacggcctggtgaactgcaactggctgttcctg
aagtctgtgccccacttctccatggcagcaccccgtggcaatgtcaccagcctttccttgtcctccaaccgcatc
caccacctccatgattctgactttgcccacctgcccagcctgcggcatctcaacctcaagtggaactgcccgccg
gttggcctcagccccatgcacttcccctgccacatgaccatcgagcccagcaccttcttggctgtgcccaccctg
gaagagctaaacctgagctacaacaacatcatgactgtgcctgcgctgcccaaatccctcatatccctgtccctc
agccataccaacatcctgatgctagactctgccagcctcgccggcctgcatgccctgcgcttcctattcatggac
ggcaactgttattacaagaacccctgcaggcaggcactggaggtggccccgggtgccctccttggcctgggcaac
ctcacccacctgtcactcaagtacaacaacctcactgtggtgccccgcaacctgccttccagcctggagtatctg
ctgttgtcctacaaccgcatcgtcaaactggcgcctgaggacctggccaatctgaccgccctgcgtgtgctcgat
gtgggcggaaattgccgccgctgcgaccacgctcccaacccctgcatggagtgccctcgtcacttcccccagcta
catcccgataccttcagccacctgagccgtcttgaaggcctggtgttgaaggacagttctctctcctggctgaat
gccagttggttccgtgggctgggaaacctccgagtgctggacctgagtgagaacttcctctacaaatgcatcact

aaaaccaaggccttccagggcctaacacagctgcgcaagcttaacctgtccttcaattaccaaaagagggtgtcc
tttgcccacctgtctctggccccttccttcgggagcctggtcgccctgaaggagctggacatgcacggcatcttc
ttccgctcactcgatgagaccacgctccggccactggcccgcctgcccatgctccagactctgcgtctgcagatg
aacttcatcaaccaggcccagctcggcatcttcagggccttccctggcctgcgctacgtggacctgtcggacaac
cgcatcagcggagcttcggagctgacagccaccatgggggaggcagatggaggggagaaggtctggctgcagcct
ggggaccttgctccggccccagtggacactcccagctctgaagacttcaggcccaactgcagcaccctcaacttc
accttggatctgtcacggaacaacctggtgaccgtgcagccggagatgtttgcccagctctcgcacctgcagtgc
ctgcgcctgagccacaactgcatctcgcaggcagtcaatggctcccagttcctgccgctgaccggtctgcaggtg
ctagacctgtcccgcaataagctggacctctaccacgagcactcattcacggagctaccgcgactggaggccctg
gacctcagctacaacagccagccctttggcatgcagggcgtgggccacaacttcagcttcgtggctcacctgcgc
accctgcgccacctcagcctggcccacaacaacatccacagccaagtgtcccagcagctctgcagtacgtcgctg
cgggccctggacttcagcggcaatgcactgggccatatgtgggccgagggagacctctatctgcacttcttccaa
ggcctgagcggtttgatctggctggacttgtcccagaaccgcctgcacaccctcctgccccaaaccctgcgcaac
ctccccaagagcctacaggtgctgcgtctccgtgacaattacctggccttctttaagtggtggagcctccacttc
ctgcccaaactggaagtcctcgacctggcaggaaaccggctgaaggccctgaccaatggcagcctgcctgctggc
acccggctccggaggctggatgtcagctgcaacagcatcagcttcgtggcccccggcttctttttccaaggccaag
gagctgcgagagctcaaccttagcgccaacgccctcaagacagtggaccactcctggtttgggcccctggcgagt
gccctgcaaatactagatgtaagcgccaaccctctgcactgcgcctgtggggcggcctttatggacttcctgctg
gaggtgcaggctgccgtgcccggtctgcccagccgggtgaagtgtggcagtccgggccagctccagggcctcagc
atctttgcacaggacctgcgcctctgcctggatgaggccctctcctgggactgtttcgcc

In addition to the foregoing native rat, porcine, bovine, equine, and ovine TLR9 polypeptides and nucleic acid molecules encoding them, chimeric TLR9 polypeptides and nucleic acid molecules encoding them are provided by the invention. The chimeric polypeptides include at least one amino acid subsititution based on a comparison of conserved and non-conserved amino acids among at least two of rat, murine, porcine, bovine, equine, ovine, canine, feline, and human TLR9. The information contained in a multiple sequence alignment of these various TLR9 polypeptide sequences, provided for example in Figure 1, can be used to identify and select individual amino acid positions and even individual amino acids to substitute in designing a chimeric TLR9. The substitution or substitutions can be effected using methods known to those of ordinary skill in molecular biology. Nucleic acids encoding the native or chimeric polypeptides of the invention can be inserted into an expression vector and used to express TLR9 polypeptide.

A conservative amino acid substitution shall refer to a substitution of a first amino acid for a second amino acid, wherein side chains of the first amino acid and the second amino acid share similar features in terms of hydrophobicity, size, aromaticity, or tendency to alter conformation. For example, conservative amino acid substitutions generally may be made between members within each of the following groups: hydrophobic (A, I, L, M, V), neutral (C, S, T), acidic (D, E), basic (H, K, N, Q, R), and aromatic (F, W, Y). A non-conservative amino acid substitution refers to any other amino acid substitution.

An expression vector for TLR9 will include at least a nucleotide sequence coding for a TLR9, or a fragment thereof coding for a functional TLR9 polypeptide, operably linked to a gene expression sequence which can direct the expression of the TLR9 nucleic acid within a eukaryotic or prokaryotic cell. A "gene expression sequence" is any regulatory nucleotide sequence, such as a promoter sequence or promoter-enhancer combination, which facilitates the efficient transcription and translation of the nucleic acid to which it is operably linked. With respect to TLR9 nucleic acid, the "gene expression sequence" is any regulatory nucleotide sequence, such as a promoter sequence or promoter-enhancer combination, which facilitates the efficient transcription and translation of the TLR9 nucleic acid to which it is operably linked. The gene expression sequence may, for example, be a mammalian or viral promoter, such as a constitutive or inducible promoter. Constitutive mammalian promoters include, but are not limited to, the promoters for the following genes: hypoxanthine phosphoribosyl transferase (HPRT), adenosine deaminase, pyruvate kinase, β-actin promoter, and other constitutive promoters. Exemplary viral promoters which function constitutively in eukaryotic cells include, for example, promoters from the simian virus (e.g., SV40), papillomavirus, adenovirus, human immunodeficiency virus (HIV), Rous sarcoma virus (RSV), cytomegalovirus (CMV), the long terminal repeats (LTR) of Moloney murine leukemia virus and other retroviruses, and the thymidine kinase (TK) promoter of herpes simplex virus. Other constitutive promoters are known to those of ordinary skill in the art. The promoters useful as gene expression sequences of the invention also include inducible promoters. Inducible promoters are expressed in the presence of an inducing agent. For example, the metallothionein (MT) promoter is induced to promote transcription and translation in the presence of certain metal ions. Other inducible promoters are known to those of ordinary skill in the art.

In general, the gene expression sequence shall include, as necessary, 5' non-transcribing and 5' non-translating sequences involved with the initiation of transcription and translation, respectively, such as a TATA box, capping sequence, CAAT sequence, and the like. Especially, such 5' non-transcribing sequences will include a promoter region which includes a promoter sequence for transcriptional control of the operably joined nucleic acid coding sequence for a TLR9 polypeptide. The gene expression sequences optionally include enhancer sequences or upstream activator sequences as desired.

Generally a nucleic acid coding sequence and a gene expression sequence are said to be "operably linked" when they are covalently linked in such a way as to place the transcription and/or translation of the nucleic acid coding sequence under the influence or control of the gene expression sequence. Thus the TLR9 nucleic acid coding sequence and the gene expression sequence are said to be "operably linked" when they are covalently linked in such a way as to place the transcription and/or translation of the TLR9 nucleic acid coding sequence under the influence or control of the gene expression sequence. If it is desired that the TLR9 sequence be translated into a functional protein, two DNA sequences are said to be operably linked if induction of a promoter in the 5' gene expression sequence results in the transcription of the TLR9 sequence and if the nature of the linkage between the two DNA sequences does not (1) result in the introduction of a frame-shift mutation, (2) interfere with the ability of the promoter region to direct the transcription of the TLR9 sequence, or (3) interfere with the ability of the corresponding RNA transcript to be translated into a protein. Thus, a gene expression sequence would be operably linked to a TLR9 nucleic acid sequence if the gene expression sequence were capable of effecting transcription of that TLR9 nucleic acid sequence such that the resulting transcript might be translated into the desired TLR9 protein or polypeptide.

A "TLR9 ligand" as used herein refers to a molecule that specifically binds a TLR9 polypeptide. In one embodiment the TLR9 ligand specifically binds a TLR9 polypeptide corresponding to at least a ligand-binding portion of the extracellular domain of TLR9. In most instances a TLR9 ligand will also induce TLR9 signaling when contacted with TLR9 under suitable conditions. TLR9 signaling refers to TLR/IL-1R signal transduction mediated through the TLR9, as described in further detail elsewhere herein. As mentioned above, CpG nucleic acids have been reported to be TLR9 ligands, but TLR9 ligands may include other entities as well, including, for example, small molecules. As also previously mentioned, there appears to be a species-specific preference for at least certain TLR9s and certain CpG motifs. As used herein, a species-preferred CpG DNA refers to a particular CpG DNA that is optimized for signal induction by a TLR9 of a particular species. A CpG DNA that is optimized for signal induction by a TLR9 of a particular species refers to a CpG DNA having a sequence that preferentially binds to and/or induces signaling by TLR9 of that species. For example, a human-preferred CpG DNA shall refer to a CpG DNA that optimally stimulates human TLR9 to signal through its TIR domain. Likewise, a murine-preferred CpG DNA

shall refer to a CpG DNA that optimally stimulates murine TLR9 to signal through its TIR domain. Examples of human-preferred and murine-preferred CpG DNA are ODN 2006 (SEQ ID NO:58) and 1668 (SEQ ID NO:60), respectively.

The binding and species specificity of TLR9s are believed to be influenced by key amino acids present in the extracellular domain of TLR9. Key amino acids in a TLR9 as used herein refer to those amino acids which contribute significantly to ligand binding and ligand specificity of a particular TLR9 polypeptide.

A "CpG nucleic acid" or a "CpG immunostimulatory nucleic acid" as used herein is a nucleic acid containing at least one unmethylated CpG dinucleotide (cytosine-guanine dinucleotide sequence, i.e., "CpG DNA" or DNA containing a 5' cytosine followed by 3' guanine and linked by a phosphate bond) which activates a component of the immune system. The entire CpG nucleic acid can be unmethylated or portions may be unmethylated but at least the C of the 5' CG 3' must be unmethylated.

In one embodiment a CpG nucleic acid is represented by at least the formula:

$$5'\text{-}N_1X_1CGX_2N_2\text{-}3'$$

wherein X_1 and X_2 are nucleotides, N is any nucleotide, and N_1 and N_2 are nucleic acid sequences composed of from about 0-25 N's each. In some embodiments X_1 is adenine, guanine, or thymine and/or X_2 is cytosine, adenine, or thymine. In other embodiments X_1 is cytosine and/or X_2 is guanine.

Nucleic acids having modified backbones, such as phosphorothioate backbones, also fall within the class of immunostimulatory nucleic acids. U.S. Pat. Nos. 5,723,335 and 5,663,153 issued to Hutcherson, et al. and related PCT publication WO95/26204 describe immune stimulation using phosphorothioate oligonucleotide analogues. These patents describe the ability of the phosphorothioate backbone to stimulate an immune response in a non-sequence specific manner.

An immunostimulatory nucleic acid molecule, including for example a CpG DNA, may be double-stranded or single-stranded. Generally, double-stranded molecules may be more stable *in vivo*, while single-stranded molecules may have increased activity. The terms "nucleic acid" and "oligonucleotide" refer to multiple nucleotides (i.e., molecules comprising a sugar (e.g., ribose or deoxyribose) linked to a phosphate group and to an exchangeable organic base, which is either a substituted pyrimidine (e.g., cytosine (C), thymine (T) or uracil (U)) or a substituted purine (e.g., adenine (A) or guanine (G)) or a modified base. As

used herein, the terms "nucleic acid" and "oligonucleotide" refer to oligoribonucleotides as well as oligodeoxyribonucleotides. The terms shall also include polynucleosides (i.e., a polynucleotide minus the phosphate) and any other organic base-containing polymer. The terms "nucleic acid" and "oligonucleotide" also encompass nucleic acids or oligonucleotides with a covalently modified base and/or sugar. For example, they include nucleic acids having backbone sugars which are covalently attached to low molecular weight organic groups other than a hydroxyl group at the 2' position and other than a phosphate group at the 5' position. Thus modified nucleic acids may include a 2'-O-alkylated ribose group. In addition, modified nucleic acids may include sugars such as arabinose instead of ribose. Thus the nucleic acids may be heterogeneous in backbone composition thereby containing any possible combination of polymer units linked together such as peptide-nucleic acids (which have amino acid backbone with nucleic acid bases). In some embodiments the nucleic acids are homogeneous in backbone composition.

The substituted purines and pyrimidines of the immunostimulatory nucleic acids include standard purines and pyrimidines such as cytosine as well as base analogs such as C-5 propyne substituted bases. Wagner RW et al. (1996) *Nat Biotechnol* 14:840-4. Purines and pyrimidines include but are not limited to adenine, cytosine, guanine, thymine, 5-methylcytosine, 2-aminopurine, 2-amino-6-chloropurine, 2,6-diaminopurine, hypoxanthine, and other naturally and non-naturally occurring nucleobases, substituted and unsubstituted aromatic moieties.

The immunostimulatory nucleic acid is a linked polymer of bases or nucleotides. As used herein with respect to linked units of a nucleic acid, "linked" or "linkage" means two entities are bound to one another by any physicochemical means. Any linkage known to those of ordinary skill in the art, covalent or non-covalent, is embraced. Such linkages are well known to those of ordinary skill in the art. Natural linkages, which are those ordinarily found in nature connecting the individual units of a nucleic acid, are most common. The individual units of a nucleic acid may be linked, however, by synthetic or modified linkages.

Whenever a nucleic acid is represented by a sequence of letters it will be understood that the nucleotides are in 5' to 3' (or equivalent) order from left to right and that "A" denotes adenine, "C" denotes cytosine, "G" denotes guanine, "T" denotes thymidine, and "U" denotes uracil unless otherwise noted.

Immunostimulatory nucleic acid molecules useful according to the invention can be obtained from natural nucleic acid sources (e.g., genomic nuclear or mitochondrial DNA or cDNA), or are synthetic (e.g., produced by oligonucleotide synthesis). Nucleic acids isolated from existing nucleic acid sources are referred to herein as native, natural, or isolated nucleic acids. The nucleic acids useful according to the invention may be isolated from any source, including eukaryotic sources, prokaryotic sources, nuclear DNA, mitochondrial DNA, etc. Thus, the term nucleic acid encompasses both synthetic and isolated nucleic acids.

The immunostimulatory nucleic acids can be produced on a large scale in plasmids, (see *Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989) and separated into smaller pieces or administered whole. After being administered to a subject the plasmid can be degraded into oligonucleotides. One skilled in the art can purify viral, bacterial, eukaryotic, etc. nucleic acids using standard techniques, such as those employing restriction enzymes, exonucleases or endonucleases.

For use in the instant invention, the immunostimulatory nucleic acids can be synthesized *de novo* using any of a number of procedures well known in the art. For example, the β-cyanoethyl phosphoramidite method (Beaucage SL and Caruthers MH, *Tetrahedron Let* 22:1859 (1981)); nucleoside H-phosphonate method (Garegg et al., *Tetrahedron Let* 27:4051-4054 (1986); Froehler et al., *Nucl Acid Res* 14:5399-5407 (1986); Garegg et al., *Tetrahedron Let* 27:4055-4058 (1986); Gaffney et al., *Tetrahedron Let* 29:2619-2622 (1988)). These chemistries can be performed by a variety of automated oligonucleotide synthesizers available in the market.

The immunostimulatory nucleic acid may be any size of at least 6 nucleotides but in some embodiments are in the range of between 6 and 100 or in some embodiments between 8 and 35 nucleotides in size. Immunostimulatory nucleic acids can be produced on a large scale in plasmids. These may be administered in plasmid form or alternatively they can be degraded into oligonucleotides before administration.

A "stabilized immunostimulatory nucleic acid" shall mean a nucleic acid molecule that is relatively resistant to *in vivo* degradation (e.g., via an exo- or endo-nuclease). Stabilization can be a function of length or secondary structure. Nucleic acids that are tens to hundreds of kbs long are relatively resistant to *in vivo* degradation. For shorter nucleic acids, secondary structure can stabilize and increase their effect. For example, if the 3' end of an

oligonucleotide has self-complementarity to an upstream region, so that it can fold back and form a sort of stem loop structure, then the oligonucleotide becomes stabilized and therefore exhibits more activity.

Some stabilized immunostimulatory nucleic acids have a modified backbone. It has been demonstrated that modification of the oligonucleotide backbone provides enhanced activity of the immunostimulatory nucleic acids when administered *in vivo*. Nucleic acids, including at least two phosphorothioate linkages at the 5' end of the oligonucleotide and multiple phosphorothioate linkages at the 3' end, preferably 5, may provide maximal activity and protect the oligonucleotide from degradation by intracellular exo- and endo-nucleases. Other modified oligonucleotides include phosphodiester modified oligonucleotide, combinations of phosphodiester and phosphorothioate oligonucleotide, methylphosphonate, methylphosphorothioate, phosphorodithioate, and combinations thereof. Each of these combinations and their particular effects on immune cells is discussed in more detail in U.S. Pat. Nos. 6,194,388 and 6,207,646, the entire contents of which are incorporated herein by reference. It is believed that these modified oligonucleotides may show more stimulatory activity due to enhanced nuclease resistance, increased cellular uptake, increased protein binding, and/or altered intracellular localization. Both phosphorothioate and phosphodiester nucleic acids are active in immune cells.

Other stabilized immunostimulatory nucleic acids include: nonionic DNA analogs, such as alkyl- and aryl-phosphates (in which the charged phosphonate oxygen is replaced by an alkyl or aryl group), phosphodiester and alkylphosphotriesters, in which the charged oxygen moiety is alkylated. Oligonucleotides which contain diol, such as tetraethyleneglycol or hexaethyleneglycol, at either or both termini have also been shown to be substantially resistant to nuclease degradation.

Phosphorothioate nucleic acid molecules may be synthesized using automated techniques employing either phosphoramidate or H-phosphonate chemistries. Aryl- and alkyl-phosphonates can be made, e.g., as described in U.S. Pat. No. 4,469,863; and alkylphosphotriesters (in which the charged oxygen moiety is alkylated as described in U.S. Pat. No. 5,023,243 and European Patent No. 092,574) can be prepared by automated solid phase synthesis using commercially available reagents. Methods for making other DNA backbone modifications and substitutions have been described. Uhlmann E and Peyman A (1990) *Chem Rev* 90:544; Goodchild J (1990) *Bioconjugate Chem* 1:165.

Other sources of immunostimulatory nucleic acids useful according to the invention include standard viral and bacterial vectors, many of which are commercially available. In its broadest sense, a "vector" is any nucleic acid material which is ordinarily used to deliver and facilitate the transfer of nucleic acids to cells. The vector as used herein may be an empty vector or a vector carrying a gene which can be expressed. In the case when the vector is carrying a gene the vector generally transports the gene to the target cells with reduced degradation relative to the extent of degradation that would result in the absence of the vector. In this case the vector optionally includes gene expression sequences to enhance expression of the gene in target cells such as immune cells, but it is not required that the gene be expressed in the cell.

Nucleic acid-binding fragments of TLRs are believed to include the extracytoplasmic (extracellular) domain or subportions thereof, such as those which include at least an MBD motif, a CXXC motif, or both an MBD motif and a CXXC motif.

Both mouse and human TLR9 have an N-terminal extension of approximately 180 amino acids compared to other TLRs. An insertion also occurs at amino acids 253-268, which is not found in TLRs 1-6 but is present in human TLR7 and human TLR8. This insert has two CXXC motifs which participate in forming a CXXC domain. The CXXC domain resembles a zinc finger motif and is found in DNA-binding proteins and in certain specific CpG binding proteins, e.g., methyl-CpG binding protein-1 (MBD-1). Fujita N et al. (2000) *Mol Cell Biol* 20:5107-18. Both human and mouse TLR9 CXXC domains occur at aa 253-268:

CXXC motif:	GNCXXCXXXXXXCXXC	SEQ ID NO:62
Human TLR9:	GNCRRCDHAPNPCMEC	SEQ ID NO:63
Murine TLR9:	GNCRRCDHAPNPCMIC	SEQ ID NO:64

An additional motif believed to be involved in CpG binding is the MBD motif, also found in MBD-1, listed below as SEQ ID NO:53. Fujita, N et al.(2000) *Mol Cell Biol* 20:5107-18; Ohki I et al. (1999) *EMBO J* 18:6653-61. Amino acids 524-554 of hTLR9 and aa 525-555 of mTLR9 correspond to the MBD motif of MBD-1 as shown:

MBD motif:

MBD-1	R-XXXXXXX-R-X-D-X-Y-XXXXXXXXX-R-S-XXXXXX-Y	SEQ ID NO:65
hTLR9	Q-XXXXXXX-K-X-D-X-Y-XXXXXXXXX-R-L-XXXXXX-Y	SEQ ID NO:66
mTLR9	Q-XXXXXXX-K-X-D-X-Y-XXXXXXXXX-Q-L-XXXXXX-Y	SEQ ID NO:67
hTLR9	Q-VLDLSRN-K-L-D-L-Y-HEHSFTELP-R-L-EALDLS-Y	SEQ ID NO:68
mTLR9	Q-VLDLSHN-K-L-D-L-Y-HWKSFSELP-Q-L-QALDLS-Y	SEQ ID NO:69

Although the signaling functions of MBD-1 and TLR9 are quite different, the core D-X-Y is conserved and is believed to be involved in CpG binding.

According to another aspect of the invention, a screening method is provided for identifying an immunostimulatory compound. The method according to this aspect of the invention involves contacting a functional TLR9 with a test compound; detecting presence or absence of a response mediated by a TLR9 signal transduction pathway in the presence of the test compound arising as a result of an interaction between the functional TLR9 and the test compound; and determining the test compound is an immunostimulatory compound when the presence of a response mediated by the TLR9 signal transduction pathway is detected.

An immunostimulatory compound is a natural or synthetic compound that is capable of inducing an immune response when contacted with an immune cell. A TLR9 ligand that is an immunostimulatory compound is a natural or synthetic compound that is capable of inducing an immune response when contacted with an immune cell that expresses TLR9. A TLR9 ligand that is an immunostimulatory compound is also a natural or synthetic compound that is capable of inducing a TLR/IL-1R signal transduction pathway when contacted with a TLR9. Immunostimulatory compounds include but are not limited to immunostimulatory nucleic acids. The immunostimulatory compound can be, for example, a nucleic acid molecule, polynucleotide or oligonucleotide, a polypeptide or oligopeptide, a lipid or lipopolysaccharide, a small molecule.

A basis for certain of the screening assays is the presence of a functional TLR9 in a cell. The functional TLR9 in some instances is naturally expressed by a cell. In other instances, expression of the functional TLR9 can involve introduction or reconstitution of a species-specific TLR9 into a cell or cell line that otherwise lacks the TLR9 or lacks responsiveness to immunostimulatory nucleic acid, resulting in a cell or cell line capable of activating the TLR/IL-1R signaling pathway in response to contact with an

immunostimulatory nucleic acid. In yet other instances, expression of the functional TLR9 can involve introduction of a chimeric or modified TLR9 into a cell or cell line that otherwise lacks the TLR9 or lacks responsiveness to immunostimulatory nucleic acid, resulting in a cell or cell line capable of activating the TLR/IL-1R signaling pathway in response to contact with an immunostimulatory nucleic acid. Examples of cell lines lacking TLR9 or immunostimulatory nucleic acid responsiveness include, but are not limited to, 293 fibroblasts (ATCC CRL-1573), MonoMac-6, THP-1, U937, CHO, and any TLR9 knock-out. The introduction of the species-specific, chimeric or modified TLR9 into the cell or cell line is preferably accomplished by transient or stable transfection of the cell or cell line with a TLR9-encoding nucleic acid sequence operatively linked to a gene expression sequence (as described above). Methods for transient and for stable transfection of a cell are well known in the art.

The screening assays can have any of a number of possible readout systems based upon either TLR/IL-1R signaling pathway or other assays useful for assessing response to immunostimulatory nucleic acids. It has been reported that immune cell activation by CpG immunostimulatory sequences is dependent in some way on endosomal processing.

In certain embodiments, the readout for the screening assay is based on the use of native genes or, alternatively, cotransfected or otherwise co-introduced reporter gene constructs which are responsive to the TLR/IL-1R signal transduction pathway involving MyD88, TRAF, p38, and/or ERK. Häcker H et al. (1999) *EMBO J* 18:6973-6982. These pathways activate kinases including κB kinase complex and c-Jun N-terminal kinases. Thus reporter genes and reporter gene constructs particularly useful for the assays can include a reporter gene operatively linked to a promoter sensitive to NF-κB. Examples of such promoters include, without limitation, those for NF-κB, IL-1β, IL-6, IL-8, IL-12 p40, CD80, CD86, and TNF-α. The reporter gene operatively linked to the TLR-sensitive promoter can include, without limitation, an enzyme (e.g., luciferase, alkaline phosphatase, β-galactosidase, chloramphenicol acetyltransferase (CAT), etc.), a bioluminescence marker (e.g., green-fluorescent protein (GFP, U.S. Pat. No. 5,491,084), blue fluorescent protein, etc.), a surface-expressed molecule (e.g., CD25), and a secreted molecule (e.g., IL-8, IL-12 p40, TNF-α). In certain embodiments the reporter is selected from IL-8, TNF-α, NF-κB-luciferase (NF-κB-luc; Häcker H et al. (1999) *EMBO J* 18:6973-6982), IL-12 p40-luc (Murphy TL et al. (1995)

Mol Cell Biol 15:5258-5267), and TNF-luc (Häcker H et al. (1999) *EMBO J* 18:6973-6982). At least one of these reporter constructs (NF-κB-luc) is commercially available (Stratagene, La Jolla, CA). In assays relying on enzyme activity readout, substrate can be supplied as part of the assay, and detection can involve measurement of chemiluminescence, fluorescence, color development, incorporation of radioactive label, drug resistance, or other marker of enzyme activity. For assays relying on surface expression of a molecule, detection can be accomplished using FACS analysis or functional assays. Secreted molecules can be assayed using enzyme-linked immunosorbent assay (ELISA) or bioassays. Many such readout systems are well known in the art and are commercially available.

According to one embodiment of this method, comparison can be made to a reference immunostimulatory nucleic acid. The reference immunostimulatory nucleic acid may be any suitably selected immunostimulatory nucleic acid, including a CpG nucleic acid. In certain embodiments the screening method is performed using a plurality of test nucleic acids. In certain embodiments comparison of test and reference responses is based on comparison of quantitative measurements of responses in each instance.

In another aspect the invention provides a screening method for identifying species specificity of an immunostimulatory nucleic acid. The method involves contacting a TLR9 of a first species with a test immunostimulatory nucleic acid; contacting a TLR9 of a second species with the test immunostimulatory nucleic acid; measuring a response mediated by a TLR signal transduction pathway associated with the contacting the TLR9 of the first species with the test immunostimulatory nucleic acid; measuring a response mediated by the TLR signal transduction pathway associated with the contacting the TLR9 of the second species with the test immunostimulatory nucleic acid; and comparing the two responses. The TLR9 may be expressed by a cell or it may be part of a cell-free system. The TLR9 may be part of a complex, with either another TLR or with another protein, e.g., MyD88, IRAK, TRAF, IκB, NF-κB, or functional homologues and derivatives thereof. Thus for example a given ODN can be tested against a panel of human fibroblast 293 fibroblast cells transfected with TLR9 from various species and optionally cotransfected with a reporter construct sensitive to TLR/IL-1R activation pathways. Thus in another aspect, the invention provides a method for screening species selectivity with respect to a given nucleic acid sequence.

Test compounds can include but are not limited to peptide nucleic acids (PNAs), antibodies, polypeptides, carbohydrates, lipids, hormones, and small molecules. Test

compounds can further include variants of a reference immunostimulatory nucleic acid incorporating any one or combination of the substitutions described above. Test compounds can be generated as members of a combinatorial library of compounds.

In preferred embodiments, the screening methods can be performed on a large scale and with high throughput by incorporating, e.g., an array-based assay system and at least one automated or semi-automated step. For example, the assays can be set up using multiple-well plates in which cells are dispensed in individual wells and reagents are added in a systematic manner using a multiwell delivery device suited to the geometry of the multiwell plate. Manual and robotic multiwell delivery devices suitable for use in a high throughput screening assay are well known by those skilled in the art. Each well or array element can be mapped in a one-to-one manner to a particular test condition, such as the test compound. Readouts can also be performed in this multiwell array, preferably using a multiwell plate reader device or the like. Examples of such devices are well known in the art and are available through commercial sources. Sample and reagent handling can be automated to further enhance the throughput capacity of the screening assay, such that dozens, hundreds, thousands, or even millions of parallel assays can be performed in a day or in a week. Fully robotic systems are known in the art for applications such as generation and analysis of combinatorial libraries of synthetic compounds. See, for example, U.S. Pat. Nos. 5,443,791 and 5,708,158.

The following examples are provided for illustrative purposes and are not meant to be limiting in any way.

Examples

Example 1. Cloning and Sequencing of Rat, Porcine, Bovine, Equine, Ovine, Canine, and Feline TLR9

Cells and Tissues. Lymphoid tissues, primarily spleen or blood mononuclear cells (PBMC) from five mammalian species were collected: mouse, pig, bovine, rat and horse. Spleen samples were collected in RNA*later*™ (Ambion®, Austin, TX, USA), stabilized at 4°C overnight and stored at -70°C. Blood samples were centrifuged at 500 x g for 25 min at room temperature and the buffy coat, containing enriched PBMC, was then removed and stored at -70°C. The mouse specimen was used as a comparative positive control.

First-strand cDNA synthesis. Total RNA from the spleen and PBMC samples was isolated using a monophasic solution of phenol and guanidine isothiocyanate: TRIzol™ reagent (GIBCO BRL®, Burlington, ON, Canada) according to the manufacturer's instructions. First-strand cDNA was synthesized from the total RNA using SUPERSCRIPT™ II reverse transcriptase (GIBCO BRL®, Burlington, ON, Canada). Approximately 3 μg of total RNA was added to 50 pmoles of oligo(dT) primer [poly $T_{(18)}$]; the mixture was heated to 70°C for 10 min and subsequently chilled on ice. The following was added to the cooled reaction mixture: 1 μl of mixed dNTP stock containing 10 mM each dATP, dCTP, dGTP and dTTP (Amersham Pharmacia Biotech Inc., Baie de Urfe, Quebec) at neutral pH, 1X first strand buffer (50 mM Tris-HCl pH 8.3/ 75 mM KCl/ 3 mM $MgCl_2$) and 2 μl of 0.1 M DTT. The mixture was subsequently heated to 42°C for 2 min, followed by addition of 200 units of SUPERSCRIPT™ II reverse transcriptase. The reaction was carried out at 42°C for 50 min, followed by 70°C for 15 min. The first-strand cDNA was used as the template for subsequent polymerase chain reaction (PCR) amplifications.

PCR amplification. TLR9 gene was PCR amplified from each of the above-mentioned species using primers designed from known mouse and human TLR9 sequence in Genbank: Accession AF314224 and AF259262, respectively. The primers were designed using the primer design software, Clone Manager 5 (Scientific and Educational Software, Durham, NC, USA). TLR9 gene-specific primers used were:
forward primer 5'-ACCTTGCCTGCCTTCCTACCCTGTGA-3' (SEQ ID NO:37) and reverse primer 5'-GTCCGTGTGGGCCAGCACAAA-3' (SEQ ID NO:38).
The 2.7 Kbp fragment was PCR amplified using Advantage® 2 DNA polymerase mix (BD Biosciences Clontech, Palo Alto, CA, USA) according to the manufacturer's instructions. PCR reaction volumes of 25 μl contained 15 pmoles of each primer, 0.2 mM of dNTP mix and 1 μl of reverse transcription reaction. PCR amplification was conducted by initial denaturation at 94°C for 1 min followed by 30 cycles of 94°C denaturation (15 sec), 65°C annealing (45 sec) and 72°C extensions (2 min), with a final extension at 72°C for 5 min.

Cloning and sequencing. The PCR amplified fragment was treated with 500 units of T4 DNA polymerase (Amersham Pharmacia Biotech Inc., Baie de Urfe, Quebec) for 15 min at room temperature prior to cleaning the reaction with QIAquick PCR purification kit (QIAGEN Inc., Mississauga, ON, Canada). The fragment was then ligated to pZErO™ - 2

vector (Invitrogen™ Life Technologies, Burlington, ON, Canada), treated with *Eco RV* restriction enzyme, using T4 DNA Ligase (GIBCO BRL®, Burlington, ON, Canada). *E. coli* TOP 10 chemically competent cells (Invitrogen™ Life Technologies, Burlington, ON, Canada) were used to transform ligated products. Plasmids containing the 2.7 Kbp fragment were sequenced using an automated DNA sequencer, CEQ™ 2000XL DNA analysis system (Beckman Coulter Inc., Fullerton, CA, USA).

Sequences of the 2.7 Kbp fragment were derived from three clones of each species selected from independent PCR reactions to account for errors that may have been incurred during the PCR amplifications and to confirm the sequence data.

Nucleotide sequences of the rat, porcine, bovine, equine, ovine, canine, and feline TLR9 were extended and completed using standard 5' and 3' RACE PCR and primers designed using the sequences obtained from the 2.7 Kbp fragments.

Results. Nucleotide sequences of rat, porcine, bovine, equine, canine, and feline TLR9 cDNA obtained by the methods above are provided as SEQ ID NOs 3, 7, 11, 15, 19, 23, and 27, respectively. Deduced amino acid sequences are provided as SEQ ID NOs 1, 5, 9, 13, 17, 21, and 25, respectively. Deduced amino acid sequences of full-length murine and human TLR9 are provided as SEQ ID NOs 29 and 33, respectively.

Example 2. Comparison of Aligned Sequences for TLR9 from Various Mammalian Species.

Multiple sequence alignment of deduced amino acid sequences for feline, canine, bovine, mouse, ovine, porcine, horse, human, and rat TLR9 polypeptides was performed using Clustal W 1.82 (see, for example, www.cmbi.kun.nl/bioinf/tools/clustalw.shtml). In addition, paired sequence alignment of deduced amino acid sequences for murine and human TLR9 polypeptides was performed using Clustal W 1.82. The results of the multiple sequence alignment are presented in **Figure 1**. As will be appreciated from Figure 1, certain amino acids are highly conserved across all species examined. Similarly, certain amino acids differ only by conservative amino acid substitutions among the various species. In addition, it is evident that certain amino acids which are conserved between murine and human TLR9 are not conserved in other species. Furthermore, Figure 1 also indicates that certain amino acids are highly divergent across various species. The information provided by the comparison of multiple species adds significantly to the information available by comparison between only murine and human TLR9 sequences.

The putative transmembrane regions of the TLR9 polypeptides are indicated in boxes in Figure 1. Sequence upstream of each transmembrane region is extracellular domain and is believed to include sequence primarily responsible for binding to TLR9 ligands, including CpG DNA. The extracellular domains of feline, canine, bovine, mouse, ovine, porcine, horse, human, and rat TLR9 correspond to amino acids numbered 1-820, 1-822, 1-818, 1-821, 1-818, 1-819, 1-820, 1-820, and 1-821, respectively, as shown in Figure 1.

Figure 2 presents an evolutionary relatedness tree for six TLR9 polypeptides examined. The cladogram in Figure 2 was prepared using Clustal W (see above). As can be appreciated from this figure, murine and human TLR9 are nearly the most divergent TLR9s in this group. Surprisingly, human and horse TLR9 appear relatively closely related.

Example 3. Reconstitution of TLR9 Signaling in 293 Fibroblasts.

Mouse TLR9 cDNA (SEQ ID NO:31) and human TLR9 cDNA (SEQ ID NO:35) in pT-Adv vector (from Clonetech) were individually cloned into the expression vector pcDNA3.1(-) from Invitrogen using the EcoRI site. Utilizing a "gain of function" assay it was possible to reconstitute human TLR9 (hTLR9) and murine TLR9 (mTLR9) signaling in CpG-DNA non-responsive human 293 fibroblasts (ATCC, CRL-1573). The expression vectors mentioned above were transfected into 293 fibroblast cells using the calcium phosphate method.

Since NF-κB activation is central to the IL-1/TLR signal transduction pathway (Medzhitov R et al. (1998) *Mol Cell* 2:253-258; Muzio M et al. (1998) *J Exp Med* 187:2097-101), cells were transfected with hTLR9 or co-transfected with hTLR9 and an NF-κB-driven luciferase reporter construct. Human fibroblast 293 cells were transiently transfected with hTLR9 and a six-times NF-κB-luciferase reporter plasmid (NF-κB-luc) or with hTLR9 alone. After stimulus with CpG-ODN (2006, 2μM, TCGTCGTTTTGTCGTTTTGTCGTT, SEQ ID NO:58), GpC-ODN (2006-GC, 2μM, TGCTGCTTTTGTGCTTTTGTGCTT, SEQ ID NO:59), LPS (100 ng/ml) or media, NF-κB activation by luciferase readout (8h) or IL-8 production by ELISA (48h) were monitored. Results representative of three independent experiments showed that cells expressing hTLR9 responded to CpG-DNA but not to LPS.

Independently, human fibroblast 293 cells were transiently transfected with mTLR9 and the NF-κB-luc construct or with mTLR9 alone. After stimulation with CpG-ODN (1668, 2μM; TCCATGACGTTCCTGATGCT, SEQ ID NO:60), GpC-ODN (1668-GC, 2μM;

TCCATGAGCTTCCTGATGCT, SEQ ID NO:61), LPS (100 ng/ml) or media, NF-κB activation by luciferase readout (8h) or IL-8 production by ELISA (48h) were monitored. Results showed that expression of TLR9 (human or mouse) in 293 cells results in a gain of function for CpG-DNA stimulation.

To generate stable clones expressing human TLR9, murine TLR9, or either TLR9 with the NF-κB-luc reporter plasmid, 293 cells were transfected in 10 cm plates ($2x10^6$ cells/plate) with 16 μg of DNA and selected with 0.7 mg/ml G418 (PAA Laboratories GmbH, Cölbe, Germany). Clones were tested for TLR9 expression by RT-PCR. The clones were also screened for IL-8 production or NF-κB-luciferase activity after stimulation with ODN. Four different types of clones were generated.

293-hTLR9-luc: expressing human TLR9 and 6-fold NF-κB–luciferase reporter
293-mTLR9-luc: expressing murine TLR9 and 6-fold NF-κB–luciferase reporter
293-hTLR9: expressing human TLR9
293-mTLR9: expressing murine TLR9

Results indicated that stable clones also responded to CpG-ODN.

Example 4. Similar ODN Sequence Specificity of TLR9 of Human and Equine TLR9.

$3x10^6$ 293T cells were electroporated with 5μg NF-κB-luc plasmid and 5 μg of either horse TLR9-pcDNA3.1 plasmid or humanTLR9-pcDNA3.1 plasmid at 200V, 975 μF. After the electroporation the cells were plated in 96-well cell culture plates at $2.5x10^4$ cells per well and grown overnight at 37°C. The cells were stimulated with the indicated concentration of ODN for 16h, after which the supernatant was removed and the cells lysed in lysis buffer and frozen for at least 2 hours at –80°C. Luciferase activity was measured by adding Luciferase Assay substrate from Promega. Values are given as fold specific induction over non-stimulated control. Results are shown in **Figure 3**.

As shown in Figure 3, ODN 2006 (TCGTCGTTTTGTCGTTTTGTCGTT; SEQ ID NO:58) has a strong specificity for human TLR9. ODN 1982 (TCCAGGACTTCTCTCAGGTT; SEQ ID NO:70) was the negative control ODN. ODN 5890 (TCCATGACGTTTTTGATGTT; SEQ ID NO:39) has a strong specificity for mouse

TLR9. This experiment demonstrates the similarity of horse TLR9 to human TLR9 in binding specificity, a result predicted by the evolutionary relatedness of horse TLR9 to human TLR9. Mouse TLR9 is more distant from horse TLR9 and human TLR9 in sequence homology, and ODN 5890 was not detected by either human or horse TLR9.

Example 5. Non-human, Non-murine Native Mammalian TLR9 Useful in Screening for Human-Preferred CpG DNA.

Native rat, porcine, bovine, equine, and ovine TLR9 polypeptides are screened for binding or TLR9 signaling activity when contacted with human-preferred CpG DNA (ODN 2006). Rat, porcine, bovine, equine, or ovine TLR9 polypeptides which exhibit significant TLR9 binding or TLR9 signaling activity in this assay are then used as the basis for screening for additional human-preferred CpG DNA. An expression vector containing a nucleic acid sequence encoding a selected native rat, porcine, bovine, equine, or ovine TLR9 polypeptide, and optionally a reporter construct, is introduced into cells which do not express TLR9. The cells expressing the selected native rat, porcine, bovine, equine, or ovine TLR9 polypeptide are contacted with candidate human-preferred CpG DNA. Candidate human-preferred CpG DNA exhibiting significant TLR9 binding or TLR9 signaling activity are selected as human-preferred CpG DNA.

Example 6. Chimeric TLR9 Useful in Screening for Human-Preferred CpG DNA.

Chimeric TLR9 polypeptides are screened for binding or TLR9 signaling activity when contacted with human-preferred CpG DNA (ODN 2006). Chimeric TLR9 polypeptides which exhibit significant TLR9 binding or TLR9 signaling activity in this assay are then used as the basis for screening for additional human-preferred CpG DNA. An expression vector containing a nucleic acid sequence encoding a selected chimeric TLR9 polypeptide, and optionally a reporter construct, is introduced into cells which do not express TLR9. The cells expressing the selected chimeric TLR9 polypeptide are contacted with candidate human-preferred CpG DNA. Candidate human-preferred CpG DNA exhibiting significant TLR9 binding or TLR9 signaling activity are selected as human-preferred CpG DNA.

Example 7. Chimeric TLR9 Responsive to Both Human-Preferred and Murine-Preferred CpG DNA.

Chimeric TLR9 polypeptides are screened for binding or TLR9 signaling activity when contacted with human-preferred CpG DNA (ODN 2006) and also screened for binding or TLR9 signaling activity when contacted with murine-preferred CpG DNA (ODN 1668). Chimeric TLR9 polypeptides which exhibit significant TLR9 binding or TLR9 signaling activity in each of these assays are then used as the basis for screening for additional human-preferred CpG DNA and for screening for additional murine-preferred CpG DNA. An expression vector containing a nucleic acid sequence encoding a selected chimeric TLR9 polypeptide, and optionally a reporter construct, is introduced into cells which do not express TLR9. The cells expressing the selected chimeric TLR9 polypeptide are contacted with candidate human-preferred CpG DNA or candidate murine-preferred CpG DNA. Candidate human-preferred CpG DNA exhibiting significant TLR9 binding or TLR9 signaling activity are selected as human-preferred CpG DNA. Candidate murine-preferred CpG DNA exhibiting significant TLR9 binding or TLR9 signaling activity are selected as murine-preferred CpG DNA.

Equivalents

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by examples provided, since the examples are intended as a single illustration of one aspect of the invention and other functionally equivalent embodiments are within the scope of the invention. Various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims. The advantages of the invention are not necessarily encompassed by each embodiment of the invention.

All references, patents and patent publications that are recited in this application are incorporated in their entirety herein by reference.

We claim:

Claims

1. An isolated polypeptide comprising an amino acid sequence selected from the group SEQ ID NO:1, SEQ ID NO:5, SEQ ID NO:9, SEQ ID NO:13, and SEQ ID NO:17.

2. An isolated polypeptide comprising an amino acid sequence selected from the group SEQ ID NO:2, SEQ ID NO:6, SEQ ID NO:10, SEQ ID NO:14, and SEQ ID NO:18.

3. An isolated nucleic acid molecule comprising a nucleic acid sequence encoding a polypeptide comprising an amino acid sequence selected from the group SEQ ID NO:1, SEQ ID NO:5, SEQ ID NO:9, SEQ ID NO:13, and SEQ ID NO:17.

4. An isolated nucleic acid molecule comprising a nucleic acid sequence encoding a polypeptide comprising an amino acid sequence selected from the group SEQ ID NO:2, SEQ ID NO:6, SEQ ID NO:10, SEQ ID NO:14, and SEQ ID NO:18.

5. A vector comprising the nucleic acid of any of claims 3-4.

6. A cell comprising the vector of claim 5.

7. An antibody or fragment thereof that binds specifically to the polypeptide of any of claims 1-2.

8. A method for identifying key amino acids in a TLR9 of a first species which confer specificity for CpG DNA optimized for TLR9 of the first species, comprising:

aligning protein sequences of TLR9 of a first species, TLR9 of a second species, and TLR9 of a third species, wherein the TLR9 of the third species preferentially generates a signal when contacted with a CpG DNA optimized for TLR9 of the first species rather than when contacted with a CpG DNA optimized for TLR9 of the second species;

generating an initial set of candidate amino acids in the TLR9 of the first species by excluding each amino acid in the TLR9 of the first species which (a) is identical with the

TLR9 of the second species or (b) differs from the TLR9 of the second species only by conservative amino acid substitution;

generating a refined set of candidate amino acids by selecting each amino acid in the initial set of candidate amino acids in the TLR9 of the first species which (a) is identical with the TLR9 of the third species or (b) differs from the TLR9 of the third species only by conservative amino acid substitution; and

identifying as key amino acids in the TLR9 of the first species each amino acid in the refined set of candidate amino acids.

9. A method for identifying key amino acids in human TLR9 which confer specificity for CpG DNA optimized for human TLR9, comprising:

aligning protein sequences of human TLR9, murine TLR9, and TLR9 of a third species, wherein the TLR9 of the third species preferentially generates a signal when contacted with a CpG DNA optimized for human TLR9 rather than when contacted with a CpG DNA optimized for murine TLR9;

generating an initial set of candidate amino acids in human TLR9 by excluding each amino acid in human TLR9 which (a) is identical with murine TLR9 or (b) differs from murine TLR9 only by conservative amino acid substitution;

generating a refined set of candidate amino acids by selecting each amino acid in the initial set of candidate amino acids in human TLR9 which (a) is identical with the TLR9 of the third species or (b) differs from the TLR9 of the third species only by conservative amino acid substitution; and

identifying as key amino acids in human TLR9 each amino acid in the refined set of candidate amino acids.

10. The method according to claim 9, performed iteratively with a plurality of TLR9s derived from different species other than human and mouse, wherein for each TLR9 the refined set of candidate amino acids is assigned a weight, said weight corresponding to a ratio equal to (responsiveness to human-preferred CpG DNA)/(responsiveness to murine-preferred CpG DNA).

11. An isolated polypeptide comprising an amino acid sequence identical to SEQ ID NO:30 except for substitution of at least one key amino acid identifed according to the method of any of claims 9 or 10.

12. An isolated nucleic acid molecule comprising a nucleic acid sequence encoding a polypeptide according to claim 11.

13. A vector comprising the nucleic acid of claim 12.

14. A cell comprising the vector of claim 13.

15. An antibody that binds specifically to the polypeptide of claim 14.

16. A screening method to identify a TLR9 ligand, comprising:

contacting a polypeptide according to any of claims 1, 2, or 11 with a candidate TLR9 ligand;

measuring a signal in response to the contacting; and

identifying the candidate TLR9 ligand as a TLR9 ligand when the signal in response to the contacting is consistent with TLR9 signaling.

17. The method of claim 16, wherein the signal comprises expression of a reporter gene responsive to TLR/IL-1R signal transduction pathway.

18. The method of claim 17, wherein the reporter gene is operatively linked to a promoter sensitive to NF-κB.

19. The method of claim 17, wherein the candidate TLR9 ligand is an immunostimulatory nucleic acid.

20. The method of claim 19, wherein the immunostimulatory nucleic acid is CpG DNA.

21. A screening method to identify species-specific CpG-motif preference of an isolated polypeptide of claim 2 or claim 11, comprising:

contacting an isolated polypeptide of claim 2 or claim 11 with a CpG DNA comprising a hexamer sequence selected from the group consisting of GACGTT, AACGTT, CACGTT, TACGTT, GGCGTT, GCCGTT, GTCGTT, GATGTT, GAAGTT, GAGGTT, GACATT, GACCTT, GACTTT, GACGCT, GACGAT, GACGGT, GACGTC, GACGTA, and GACGTG;

measuring a signal in response to the contacting; and

identifying a species-specific CpG-motif preference when the signal in response to the contacting is consistent with TLR9 signaling.

22. The method of claim 21, wherein the signal comprises expression of a reporter gene responsive to TLR/IL-1R signal transduction pathway.

23. The method of claim 17, wherein the reporter gene is operatively linked to a promoter sensitive to NF-κB.

24. The method of claim 21, wherein the CpG DNA is an oligodeoxynucleotide having a sequence selected from the group consisting of

TCCATGACGTTTTTGATGTT	(SEQ ID NO:39),
TCCATAACGTTTTTGATGTT	(SEQ ID NO:40),
TCCATCACGTTTTTGATGTT	(SEQ ID NO:41),
TCCATTACGTTTTTGATGTT	(SEQ ID NO:42),
TCCATGGCGTTTTTGATGTT	(SEQ ID NO:43),
TCCATGCCGTTTTTGATGTT	(SEQ ID NO:44),
TCCATGTCGTTTTTGATGTT	(SEQ ID NO:45),
TCCATGATGTTTTTGATGTT	(SEQ ID NO:46),
TCCATGAAGTTTTTGATGTT	(SEQ ID NO:47),
TCCATGAGGTTTTTGATGTT	(SEQ ID NO:48),
TCCATGACATTTTTGATGTT	(SEQ ID NO:49),
TCCATGACCTTTTTGATGTT	(SEQ ID NO:50),
TCCATGACTTTTTTGATGTT	(SEQ ID NO:51),
TCCATGACGCTTTTGATGTT	(SEQ ID NO:52),
TCCATGACGATTTTGATGTT	(SEQ ID NO:53),
TCCATGACGGTTTTGATGTT	(SEQ ID NO:54),
TCCATGACGTCTTTGATGTT	(SEQ ID NO:55),
TCCATGACGTATTTGATGTT	(SEQ ID NO:56), and
TCCATGACGTGTTTGATGTT	(SEQ ID NO:57).

Figure 1
(1/3)

```
feline      MGPCHGALHPLSLLVQAAALAVALAQGTLPAFLPCELQRHGLVNCDWLFLKSVPHFSAAA 60
canine      MGPCRGALHPLSLLVQAAALALALAQGTLPAFLPCELQPHGLVNCNWLFLKSVPRFSAAA 60
bovine      MGP-YCAPHPLSLLVQAAALAAALAEGTLPAFLPCELQPHGQVDCNWLFLKSVPHFSAGA 59
mouse       MGP-YCAPHPLSLLVQAAALAAALAEGTLPAFLPCELQPHGQVDCNWLFLKSVPHFSAGA 59
ovine       MGP-YCAPHPLSLLVQAAALAAALAQGTLPAFLPCELQPRGKVNCNWLFLKSVPRFSAGA 59
porcine     MGP-RCTLHPLSLLVQVTALAAALAQGRLPAFLPCELQPHGLVNCNWLFLKSVPHFSAAA 59
horse       MGPCHGALQPLSLLVQAAMLAVALAQGTLPPFLPCELQPHGLVNCNWLFLKSVPHFSAAA 60
human       MGFCRSALHPLSLLVQAIMLAMTLALGTLPAFLPCELQPHGLVNCNWLFLKSVPHFSMAA 60
rat         MVLCRRTLHPLSLLVQAAVLAEALALGTLPAFLPCELKPHGLVDCNWLFLKSVPHFSAAE 60
            *     : :*******.  ** :** * **.******: :* *:*:********:** .

feline      PRGNVTSLSLYSNRIHHLHDSDFVHLSSLRRLNLKWNCPPASLSPMHFPCHMTIEPHTFL 120
canine      PRGNVTSLSLYSNRIHHLHDYDFVHFVHLRRLNLKWNCPPASLSPMHFPCHMTIEPNTFL 120
bovine      PRANVTSLSLISNRIHHLHDSDFVHLSNLRVLNLKWNCPPAGLSPMHFPCRMTIEPNTFL 119
mouse       PRANVTSLSLISNRIHHLHDSDFVHLSNLRVLNLKWNCPPAGLSPMHFPCRMTIEPNTFL 119
ovine       PRANVTSLSLISNRIHHLHDSDFVHLSNLRVLNLKWNCPPAGLSPMHFPCRMTIEPNTFL 119
porcine     PRANVTSLSLLSNRIHHLHDSDFVHLSSLRTLNLKWNCPPAGLSPMHFPCHMTIEPNTFL 119
horse       PRDNVTSLSLLSNRIHHLHDSDFAQLSNLQKLNLKWNCPPAGLSPMHFPCHMTIEPNTFL 120
human       PRGNVTSLSLSSNRIHHLHDSDFAHLPSLRHLNLKWNCPPVGLSPMHFPCHMTIEPSTFL 120
rat         PRSNITSLSLIANRIHHLHNLDFVHLPNVRQLNLKWNCPPPGLSPLHFSCRMTIEPKTFL 120
            ** *:***** :*******: **.::  :: ********* .***:**.*:***** ***

feline      AVPTLEELNLSYNSITTVPALPSSLVSLSLSRTNILVLDPANLAGLHSLRFLFLDGNCYY 180
canine      AVPTLEDLNLSYNSITTVPALPSSLVSLSLSRTNILVLDPATLAGLYALRFLFLDGNCYY 180
bovine      AVPTLEELNLSYNGITTVPALPSSLVSLSLSHTSILVLGPTHFTGLHALRFLYMDGNCYY 179
mouse       AVPTLEELNLSYNGITTVPALPSSLVSLSLSHTSILVLGPTHFTGLHALRFLYMDGNCYY 179
ovine       AVPTLEELNLSYNGITTVPALPSSLVSLSLSRTSILVLGPTHFTGLHALRFLYMDGNCYY 179
porcine     AVPTLEELNLSYNSITTVPALPDSLVSLSLSRTNILVLDPTHLTGLHALRYLYMDGNCYY 179
horse       AVPTLEELNLSYNGITTVPALPSSLVSLILSRTNILQLDPTSLTGLHALRFLYMDGNCYY 180
human       AVPTLEELNLSYNNIMTVPALPKSLISLSLSHTNILMLDSASLAGLHALRFLFMDGNCYY 180
rat         AMRMLEELNLSYNGITTVPRLPSSLTNLSLSHTNILVLDASSLAGLHSLRVLFMDGNCYY 180
            *:  **:******.* *** **.** .* **:*.** *..: ::**::** *::******

feline      KNPCPQALQVAPGALLGLGNLTHLSLKYNNLTAVPRGLPPSLEYLLLSYNHIITLAPEDL 240
canine      KNPCQQALQVAPGALLGLGNLTHLSLKYNNLTVVPRGLPPSLEYLLLSYNHIITLAPEDL 240
bovine      MNPCPRALEVAPGALLGLGNLTHLSLKYNNLTEVPRRLPPSLDTLLLSYNHIVTLAPEDL 239
mouse       MNPCPRALEVAPGALLGLGNLTHLSLKYNNLTEVPRRLPPSLDTLLLSYNHIVTLAPEDL 239
ovine       KNPCQQAVEVAPGALLGLGNLTHLSLKYNNLTEVPRRLPPSLDTLLLSYNHIITLAPEDL 239
porcine     KNPCQGALEVVPGALLGLGNLTHLSLKYNNLTEVPRSLPPSLETLLLSYNHIVTLTPEDL 239
horse       KNPCGRALEVAPGALLGLGNLTHLSLKYNNLTTVPRSLPPSLEYLLLSYNHIVTLAPEDL 240
human       KNPCRQALEVAPGALLGLGNLTHLSLKYNNLTVVPRNLPSSLEYLLLSYNRIVKLAPEDL 240
rat         KNPCNGAVNVTPDAFLGLSNLTHLSLKYNNLTEVPRQLPPSLEYLLLSYNLIVKLGAEDL 240
             ***  *::*.*.*:***.************** *** **.**: ****** *:.* .***

feline      ANLTALRVLDVGGNCRRCDHARNPCMECPKGFPHLHPDTFSHLNHLEGLVLKDSSLYNLN 300
canine      ANLTALRVLDVGGNCRRCDHARNPCRECPKGFPQLHPNTFGHLSHLEGLVLRDSSLYSLD 300
bovine      ANLTALRVLDVGGNCRRCDHARNPCRECPKNFPKLHPDTFSHLSRLEGLVLKDSSLYKLE 299
mouse       ANLTALRVLDVGGNCRRCDHARNPCRECPKNFPKLHPDTFSHLSRLEGLVLKDSSLYKLE 299
ovine       ANLTALRVLDVGGNCRRCDHARNPCRECPKNFPKLHPDTFSHLSRLEGLVLKDSSLYKLE 299
porcine     ANLTALRVLDVGGNCRRCDHARNPCRECPKDHPKLHSDTFSHLSRLEGLVLKDSSLYNLD 299
horse       ANLTALRVLDVGGNCRRCDHARNPCVECPHKFPQLHSDTFSHLSRLEGLVLKDSSLYQLN 300
human       ANLTALRVLDVGGNCRRCDHAPNPCMECPRHFPQLHPDTFSHLSRLEGLVLKDSSLSWLN 300
rat         ANLTSLRMLDVGGNCRRCDHAPDLCTECRQKSLDLHPQTFHHLSHLEGLVLKDSSLHSLN 300
            ****:**:************** : * ** :   .**.:** **.:*******:****  *:

feline      PRWFHALGNLMVLDLSENFLYDCITKTTAFQGLAQLRRLNLSFNYHKKVSFAHLHLAPSF 360
canine      PRWFHGLGNLMVLDLSENFLYDCITKTKAFYGLARLRRLNLSFNYHKKVSFAHLHLASSF 360
bovine      KDWFRGLGRLQVLDLSENFLYDYITKTTIFNDLTQLRRLNLSFNYHKKVSFAHLHLASSF 359
mouse       KDWFRGLGRLQVLDLSENFLYDYITKTTIFNDLTQLRRLNLSFNYHKKVSFAHLHLASSF 359
ovine       KDWFRGLGRLQVLDLSENFLYDYITKTTIFRNLTQLRRLNLSFNYHKKVSFAHLQLAPSF 359
porcine     TRWFRGLDRLQVLDLSENFLYDCITKTTAFQGLARLRSLNLSFNYHKKVSFAHLHLAPSF 359
horse       PRWFRGLGNLTVLDLSENFLYDCITKTKAFQGLAQLRRLNLSFNYHKKVSFAHLTLAPSF 360
human       ASWFRGLGNLRVLDLSENFLYKCITKTKAFQGLTQLRKLNLSFNYQKRVSFAHLSLAPSF 360
rat         SKWFQGLANLSVLDLSENFLYESINKTSAFQNLTRLRKLDLSFNYCKKVSFARLHLASSF 360
              **:.* .* **********. *.**. * .*::** *:***** *:****:* **.**
```

Figure 1
(2/3)

```
feline      GSLLSLQQLDMHGIFFRSLSETTLRSLVHLPMLQSLHLQMNFINQAQLSIFGAFPGLRYV 420
canine      GSLLSLQELDIHGIFFRSLSKTTLQSLAHLPMLQRLHLQLNFISQAQLSIFGAFPGLRYV 420
bovine      GSLVSLEKLDMHGIFFRSLTNITLQSLTRLPKLQSLHLQLNFINQAQLSIFGAFPSLLFV 419
mouse       GSLVSLEKLDMHGIFFRSLTNITLQSLTRLPKLQSLHLQLNFINQAQLSIFGAFPSLLFV 419
ovine       GGLVSLEKLDMHGIFFRSLTNTTLRPLTQLPKLQSLSLQLNFINQAELSIFGAFPSLLFV 419
porcine     GHLRSLKELDMHGIFFRSLSETTLQPLVQLPMLQTLRLQMNFINQAQLSIFGAFPGLLYV 419
horse       GSLLSLQELDMHGIFFRSLSQKTLQPLARLPMLQRLYLQMNFINQAQLGIFKDFPGLRYI 420
human       GSLVALKELDMHGIFFRSLDETTLRPLARLPMLQTLRLQMNFINQAQLGIFRAFPGLRYV 420
rat         KSLVSLQELNMNGIFFRLLNKNTLRWLAGLPKLHTLHLQMNFINQAQLSVFSTFRALRFV 420
              * :*::*:::***** * : **: *. ** *: * **:***.**:*.:*  * .* ::

feline      DLSDNRISGAMELAAATGEVDG--GERVRLPSGDLALGPPGTPSSEGFMPGCKTLNFTLD 478
canine      DLSDNRISGAAEPAAATGEVEADCGERVWPQSRDLALGPLGTPGSEAFMPSCRTLNFTLD 480
bovine      DLSDNRISGAATPAAALGEVDS--RVEVWRLPRGLAPGPLDAVSSKDFMPSCN-LNFTLD 476
mouse       DLSDNRISGAATPAAALGEVDS--RVEVWRLPRGLAPGPLDAVSSKDFMPSCN-LNFTLD 476
ovine       DLSDNRISGAARPVAALGEVDS--GVEVWRWPRGLAPGPLAAVSAKDFMPSCN-LNFTLD 476
porcine     DLSDNRISGAARPVAITREVDG--RERVWLPSRNLAPRPLDTLRSEDFMPNCKAFSFTLD 477
horse       DLSDNRISGAVEPVATTGEVDG--GKKVWLTSRDLTPGPLDTPSSEDFMPSCKNLSFTLD 478
human       DLSDNRISGASELTATMGEADG--GEKVWLQPGDLAPAPVDTPSSEDFRPNCSTLNFTLD 478
rat         DLSNNRISGPPTLSRVAPEKAD-EAEKGVPWPASLTPALPSTPVSKNFMVRCKNLRFTMD 479
            ***:*****.         *       .    . .*:     :  :: *   *  : **:*

feline      LSRNNLVTIQPEMFARLSRLQCLLLSRNSISQAVNGSQFMPLTSLQVLDLSHNKLDLYHG 538
canine      LSRNNLVTVQPEMFVRLARLQCLGLSHNSISQAVNGSQFVPLSNLRVLDLSHNKLDLYHG 540
bovine      LSRNNLVTIQQEMFTRLSRLQCLRLSHNSISQAVNGSQFVPLTSLRVLDLSHNKLDLYHG 536
mouse       LSRNNLVTIQQEMFTRLSRLQCLRLSHNSISQAVNGSQFVPLTSLRVLDLSHNKLDLYHG 536
ovine       LSRNNLVTIQQEMFTRLSRLQCLRLSHNSISQAVNGSQFVPLTRLRVLDLSYNKLDLYHG 536
porcine     LSRNNLVTIQSEMFARLSRLECLRLSHNSISQAVNGSQFVPLTSLRVLDLSHNKLDLYHG 537
horse       LSRNNLVTVQPEMFAQLSRLQCLRLSHNSISQAVNGSQFVPLTSLQVLDLSHNKLDLYHG 538
human       LSRNNLVTVQPEMFAQLSHLQCLRLSHNCISQAVNGSQFLPLTGLQVLDLSHNKLDLYHE 538
rat         LSRNNQVTIKPEMFVNLSHLQCLSLSHNCIAQAVNGSQFLPLTNLKVLDLSYNKLDLYHS 539
            ***** **:: ***..*:::*:** **:*.*:********:**: *:*****:*******

feline      RSFTELPRLEALDLSYNSQPFSMQGVGHNLSFVAQLPALRYLSLAHNDIHSRVSQQLCSA 598
canine      RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA 600
bovine      RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596
mouse       RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596
ovine       RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596
porcine     RSFTELPRLEALDLSYNSQPFTMQGVGHNLSFVAQLPALRYLSLAHNDIHSRVSQQLCSA 597
horse       RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598
human       HSFTELPRLEALDLSYNSQPFGMQGVGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST 598
rat         KSFSELPQLQALDLSYNSQPFSMQGIGHNFSFLANLSRLQNLSLAHNDIHSRVSSRLYST 599
            :**:***:*:*********** *:*:***:**:*:*  *: ******.***:**.:* *:

feline      SLRALDFSGNALSRMWAEGDLYLHFFRGLRSLVRLDLSQNRLHTLLPRTLDNLPKSLRLL 658
canine      SLRALDFSGNTLSQMWAEGDLYLRFFQGLRSLVQLDLSQNRLHTLLPRNLDNLPKSLRLL 660
bovine      SLRALDFSGNSLSQMWAEGDLYLCFFKGLRNLVQLDLSENHLHTLLPRHLDNLPKSLRQL 656
mouse       SLRALDFSGNSLSQMWAEGDLYLCFFKGLRNLVQLDLSENHLHTLLPRHLDNLPKSLRQL 656
ovine       SLRALDFSGNSLSQMWAEGDLYLCFFKGLRNLVQLDLSKNHLHTLLPRHLDNLPKSLRQL 656
porcine     SLCALDFSGNDLSRMWAEGDLYLRFFQGLRSLVWLDLSQNHLHTLLPRALDNLPKSLKHL 657
horse       SLWALDFSGNSLSQMWAEGDLYLRFFQGLRSLIRLDLSQNRLHTLLPCTLGNLPKSLQLL 658
human       SLRALDFSGNALGHMWAEGDLYLHFFQGLSGLIWLDLSQNRLHTLLPQTLRNLPKSLQVL 658
rat         SVEYLDFSGNGVGRMWDEEDLYLYFFQDLRSLIHLDLSQNKLHILRPQNLNYLPKSLTKL 659
            *:  ****** :.:** * **** **:.* .*: ****:*:** * *  *  ***** *

feline      RLRDNYLAFFNWSSLVLLPRLEALDLAGNQLKALSNGSLPNGTQLQRLDLSSNSISFVAS 718
canine      RLRDNYLAFFNWSSLALLPKLEALDLAGNQLKALSNGSLPNGTQLQRLDLSGNSIGFVVP 720
bovine      RLRDNNLAFFNWSSLTVLPRLEALDLAGNQLKALSNGSLPPGIRLQKLDVSSNSIGFVIP 716
mouse       RLRDNNLAFFNWSSLTVLPRLEALDLAGNQLKALSNGSLPPGIRLQKLDVSSNSIGFVIP 716
ovine       RLRDNNLAFFNWSSLTVLPQLEALDLAGNQLKALSNGSLPPGTRLQKLDVSSNSIGFVTP 716
porcine     HLRDNNLAFFNWSSLTLLPKLETLDLAGNQLKALSNGSLPSGTQLRRLDLSGNSIGFVNP 717
horse       RLRNNYLAFFNWSSLTLLPNLETLDLAGNQLKALSNGSLPSGTQLQRLDVSRNSIIFVVP 718
human       RLRDNYLAFFKWWSLHFLPKLEVLDLAGNQLKALTNGSLPAGTRLRRLDVSCNSISFVAP 718
rat         SFRDNHLSFFNWSSLAFLPNLRDLDLAGNLLKALTNGTLPNGTLLQKLDVSSNSIVFVVP 719
             :*:* *:**:* ** .**.*. ****** ****:**:** *  *::**:* *** ** .
```

Figure 1
(3/3)

```
feline      SFFALATRLRELNLSANALKTVEPSWFGSLAGTLKVLDVTGNPLHCACGAAFVDFLLEVQ 778
canine      SFFALAVRLRELNLSANALKTVEPSWFGSLAGALKVLDVTANPLHCACGATFVDFLLEVQ 780
bovine      GFFVRATRLIELNLSANALKTVDPSWFGSLAGTLKILDVSANPLHCACGAAFVDFLLERQ 776
mouse       GFFVRATRLIELNLSANALKTVDPSWFGSLAGTLKILDVSANPLHCACGAAFVDFLLERQ 776
ovine       GFFVLANRLKELNLSANALKTVDPFWFGRLTETLNILDVSANPLHCACGAAFVDFLLEMQ 776
porcine     GFFALAKQLEELNLSANALKTVEPSWFGSMVGNLKVLDVSANPLHCACGATFVGFLLEVQ 777
horse       GFFALATRLRELNLSANALRTEEPSWFGFLAGSLEVLDVSANPLHCACGAAFVDFLLQVQ 778
human       GFFSKAKELRELNLSANALKTVDHSWFGPLASALQILDVSANPLHCACGAAFMDFLLEVQ 778
rat         AFFALAVELKEVNLSHNILKTVDRSWFGPIVMNLTVLDVSSNPLHCACGAPFVDLLLEVQ 779
            .**  * .* *:*** * *:* :  *** :.  * :***:.*********.*:.:**: *

feline      AAVPGLPGHVKCGSPGQLQGRSIFAQDLRLCLDEALSWDCFGLSLLTVALGLAVPMLHHL 838
canine      AAVPGLPSRVKCGSPGQLQGRSIFAQDLRLCLDEALSWVCFSLSLLAVALSLAVPMLHQL 840
bovine      EAVPGLSRRVTCGSPGQLQGRSIFTQDLRLCLDETLSLDCFGLSLLMVALGLAVPMLHHL 836
mouse       EAVPGLSRRVTCGSPGQLQGRSIFTQDLRLCLDETLSLDCFGLSLLMVALGLAVPMLHHL 836
ovine       AAVPGLSRRVTCGSPGQLQGRSIFAQDLRLCLDETLSLDCFGFSLLMVALGLAVPMLHHL 836
porcine     AAVPGLPSRVKCGSPGQLQGHSIFAQDLRLCLDETLSWNCFGISLLLAMALGLVVPMLHHL 837
horse       AAVPGLPSRVKCGSPGQLQGRSIFAQDLRLCLDKSLSWDCFGLSLLVVALGLAMPMLHHL 838
human       AAVPGLPSRVKCGSPGQLQGLSIFAQDLRLCLDEALSWDCFALSLLAVALGLGVPMLHHL 838
rat         TKVPGLANGVKCGSPRQLQGRSIFAQDLRLCLDDVLSRDCFGLSLLAVAVGTVLPLLQHL 839
              ****.  *.**** **** ***:********. **  **.:*** :*:.  :*:*::*

feline      CGWDLWYCFHLCLAWLPRRGRR--RGADALPYDAFVVFDKAQSAVADWVYNELRVRLEER 896
canine      CGWDLWYCFHLCLAWLPRRGRR--RGVDALAYDAFVVFDKAQSSVADWVYNELRVQLEER 898
bovine      CGWDLWYCFHLCLAHLPRRRRQ--RGEDTLLYDAVVVFDKVQSAVADWVYNELRVQLEER 894
mouse       CGWDLWYCFHLCLAHLPRRRRQ--RGEDTLLYDAVVVFDKVQSAVADWVYNELRVQLEER 894
ovine       CGWDLWYCFHLCLAHLPRRRRQ--RGEDTLLYDAFVVFDKAQSAVADWVYNELRVQLEER 894
porcine     CGWDLWYCFHLCLAWLPHRGQR--RGADALFYDAFVVFDKAQSAVADWVYNELRVQLEER 895
horse       CGWDLWYCFHLGLAWLPRRGWQ--RGADALSYDAFVVFDKAQSAVADWVYNELRVRLEER 896
human       CGWDLWYCFHLCLAWLPWRGRQSGRDEDALPYDAFVVFDKTQSAVADWVYNELRGQLEEC 898
rat         CGWDVWYCFHLCLAWLPLLTRGR-RSAQALPYDAFVVFDKAQSAVADWVYNELRVRLEER 898
            ****:****** ** **       *. ::* ***.*****.**:********** :***

feline      RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL 956
canine      RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL 958
bovine      RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL 954
mouse       RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL 954
ovine       RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL 954
porcine     RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL 955
horse       RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDQVSGLLRASFLLAQQRL 956
human       RGRWALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL 958
rat         RGRRALRLCLEDRDWLPGQTLFENLWASIYGSRKTLFVLAHTDKVSGLLRTSFLLAQQRL 958
            *** *******:***:**:**********:*.*** :*** :**:******:*********

feline      LEDRKDVVVLVILRPDAHRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGTALTRDNQ 1016
canine      LEDRKDVVVLVILCPDAHRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGTALTRDNR 1018
bovine      LEDRKDVVVLVILRPAAYRSRYVRLRQRLCRQSVLLWPHQPSGQGSFWANLGIALTRDNR 1014
mouse       LEDRKDVVVLVILRPAAYRSRYVRLRQRLCRQSVLLWPHQPSGQGSFWANLGIALTRDNR 1014
ovine       LEDRKDVVVLVILRPAAYRSRYVRLRQRLCRQSVLLWPHQPSGQGSFWANLGMALTRDNR 1014
porcine     LEDRKDVVVLVILRPDAYRSRYVRLRQRLCRQSVLLWPHQPRGQGSFWAQLGTALTRDNH 1015
horse       LEDRKDVVVLVILSPDARRSRYVRLRQRLCRQSVLFWPHQPSGQRSFWAQLGMALTRDNH 1016
human       LEDRKDVVVLVILSPDGRRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGMALTRDNH 1018
rat         LEDRKDVVVLVILRPDAHRSRYVRLRQRLCRQSVLFWPHQPNGQGSFWAQLSTALTRDNH 1018
            ************* * . *****************:***** ** ****:*. ******:

feline      HFYNQNFCRGPTTAE---------------------------------------------- 1031
canine      HFYNQNFCRGPTTA----------------------------------------------- 1032
bovine      HFYNRNFCRGPTTAE---------------------------------------------- 1029
mouse       HFYNRNFCRGPTTAE---------------------------------------------- 1032
ovine       HFYNRNFCRGPTTAE---------------------------------------------- 1029
porcine     HFYNRNFCRGPTTAE---------------------------------------------- 1030
horse       HFYNQNFCRGPTMAE---------------------------------------------- 1031
human       HFYNRNFCQGPTAE----------------------------------------------- 1032
rat         HFYNRNFCRGPTAE----------------------------------------------- 1032
            ****:***:***
```

Figure 2

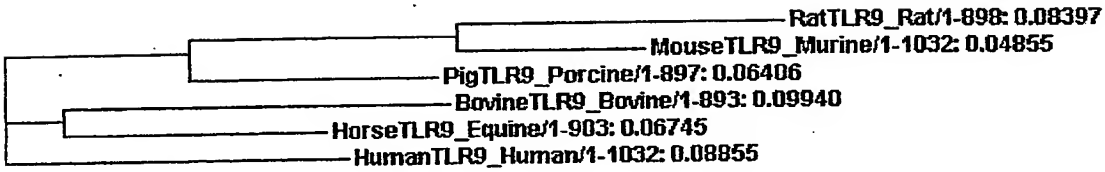


Figure 3